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THE HYDROGENOLYSIS OF CYCLIC ACETALS AND KETALS

by

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A THESIS

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ABSTRACT

A study has been made of the hydrogenolysis of cyclic acetals and ketals by lithium aluminum hydride in combination with Lewis acids.

The carbon-sulphur bond in sulphur acetals and ketals is left intact upon treatment with lithium aluminum hydride in the presence of a Lewis acid in diethyl ether, whereas the carbon-oxygen bond of hemithio- and fully oxygenated acetals and ketals is readily cleaved. This observation is explained by a mechanistic interpretation requiring the prior co-ordination of the Lewis acid with the oxygen atom of the acetal or ketal followed by a rate determining unimolecular step involving the cleavage of the complex to afford a resonance-stabilised oxo- or sulphocarbonium ion which may then be reduced by lithium aluminum hydride. An explanation for the resistance of the carbon-sulphur bond towards cleavage is offered in terms of the preferred co-ordination of the Lewis acid with the oxygen atom of either the acetal or ketal or the diethylether solvent. The less basic sulphur atom of the sulphur acetals and ketals is apparently unable to compete with the oxygen atom of the solvent for the Lewis acid.

The anomalous results obtained upon reduction of hemithioacetals and ketals with a combination of lithium aluminum hydride and boron trifluoride are explained in terms of a competition between the lithium

aluminum hydride and 1,3-oxathiolanes for reaction with the Lewis acid.

A study of the hydrogenolysis of asymmetrical, fully oxygenated cyclic acetals and ketals (1,3-dioxolanes and 1,3-dioxanes) has been undertaken, aimed at a determination of the effect of substituents at the C_2 and C_4 positions of the acetal or ketal ring upon the direction and rate of ring cleavage. The results are rationalised in terms of polar effects, electron-donating substituents accelerate while electron withdrawing substituents hinder ring cleavage. Steric factors apparently have little effect except in the cases of 2,2,4,4-tetra- and 2,2,4,4,5,5-hexasubstituted-1,3-dioxolanes. In these cases this factor is of paramount importance in determining the direction and rate of ring cleavage.

The study of the hydrogenolysis of 2,4-disubstituted-1,3-dioxolanes, in which *cis*-*trans* isomerisation is possible, revealed that *cis* and *trans* isomers differ in both the rate of their hydrogenolysis and also in the ratios of the two possible products afforded upon reductive ring cleavage.

Finally the correlation between the mechanism of hydrogenolysis of acetals and ketals with that of the acid-catalysed hydrolysis of these materials has been pointed out.

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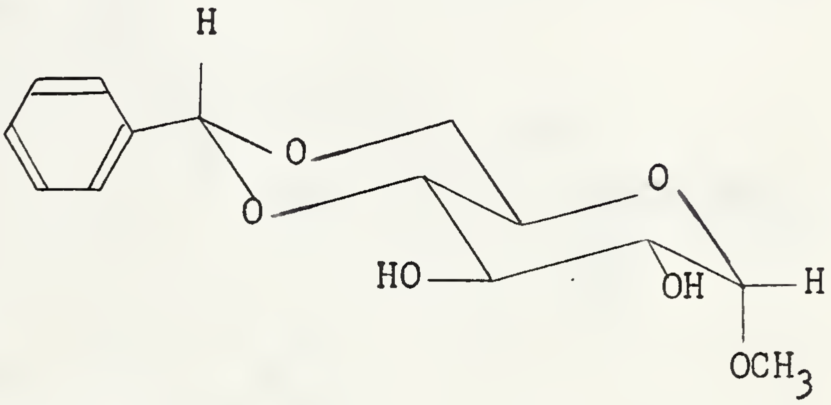
INTRODUCTION

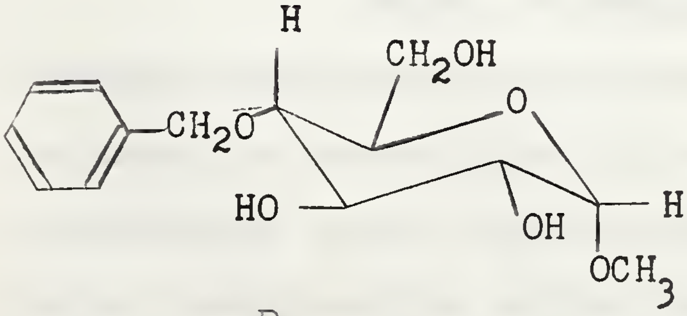
THE PROBLEM

Interest developed in the synthetic possibilities involving the selective reductive cleavage of acetals and ketals. For example the molecule methyl 4,6-O-benzylidene-α-D-glucopyranoside (A) contains two acetal structures, one involving the benzylidene group and the other the glucopyranoside unit.

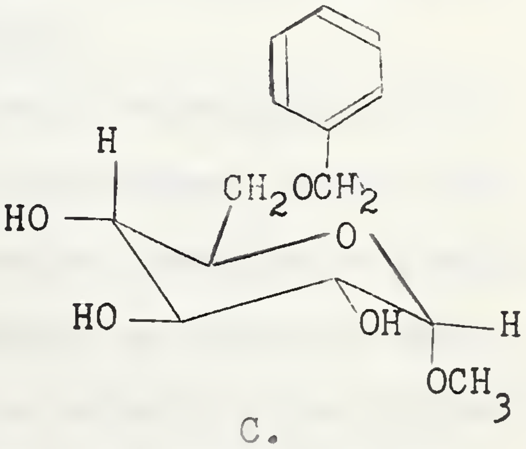


A.

Selective cleavage under reducing conditions might produce a number of possible products. Preferential attack on the benzylidene grouping might yield structure B and/or C wherein the C_6 or C_5 hydroxyl has now been blocked as a benzylether unit.

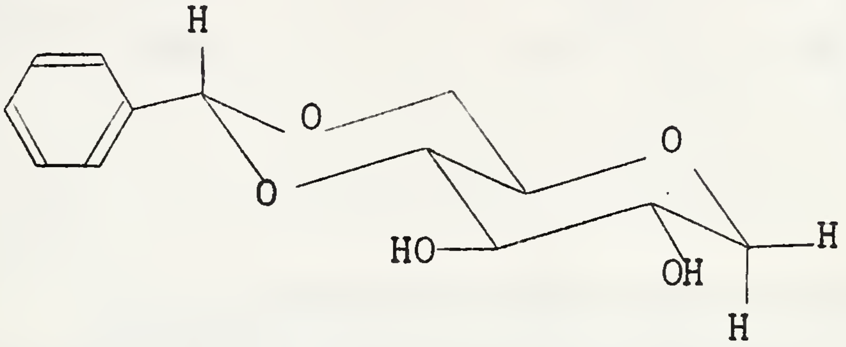


B.

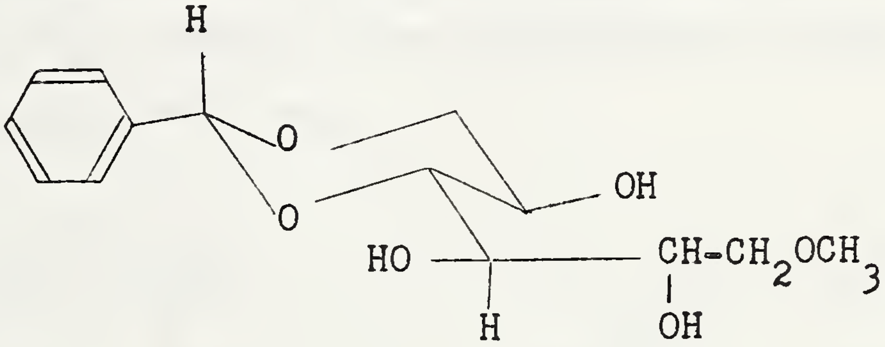


C.

Similary, selective reductive cleavage of the glycosidic linkage might yield the products D or E.



D.

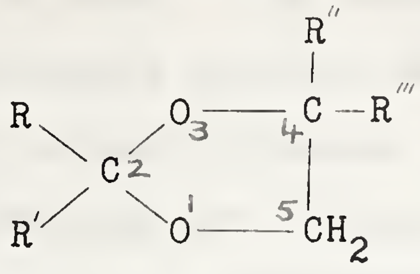


E.

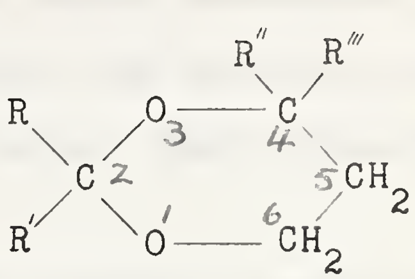
It is expected that the structural and substituent features in the acetal or ketal should have an influence on the direction of cleavage of these groups. Thus by appropriate choice of the correct acetals or ketals it might be possible to produce a number of interesting and useful derivatives of monosaccharides.

Before attempting such reductions on the somewhat complicated carbohydrate structures, it was felt necessary to investigate the reductive cleavage of simpler asymmetrical cyclic acetals and ketals in order to gain a better understanding of the factors governing the preferential cleavage of either the C_2-O_1 or the C_2-O_3 bonds in the

following systems* (F and G).

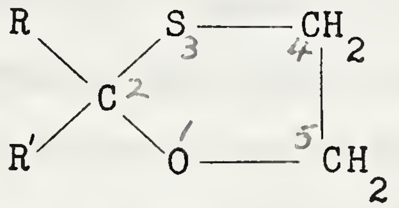


F.

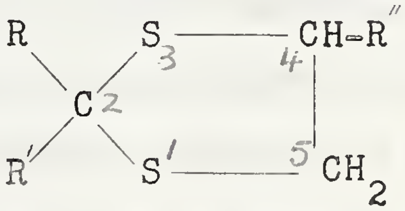


G.

As an extension to this work a study of the factors influencing the preferential cleavage of either the C_2-O or the C_2-S bonds in the corresponding sulphur compounds* (H and J) was carried out.



H.



J.

The long range aim in this study of the sulphur acetals and ketals is the possibility of selective blocking of certain hydroxyl groups in monomercaptosaccharide molecules such as 3-deoxy-3-mercapto-D-glucose. Due to the greater nucleophilicity of the mercapto group, it should be

---

* R,R′,R″ and R‴ may be any of the following groups:

H—, Alkyl—, Phenyl—, $HOCH_2$—, $ClCH_2$—, Cl_3C— and AlkylO—CH_2—.

These groups were chosen in the actual experimental work because of the ready availability of the starting materials.

preferentially involved in the first step of the formation of the acetal. The complete cyclic acetal structure then would depend upon the availability of, and structure involving, suitably situated hydroxyl groups. The structural implications are obvious.

This thesis involves a study of structural and substituent factors which control acetal and ketal reductive cleavage.

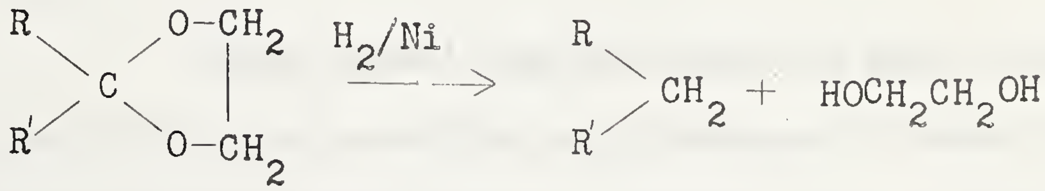
Preliminary work on the reduction of acetals and hemithioacetals showed that excellent results could be obtained by the use of a combination of lithium aluminum hydride and aluminum chloride. A few initial experiments with other reagents such as sodium in liquid ammonia, hydrazine and Raney nickel and Raney nickel alone showed that these reagents gave either complete cleavage of both of the carbon-oxygen (or sulphur) bonds or no reduction at all depending upon the acetal or reagent used. Hence the use of these reagents was discontinued and our attentions were thus confined to the study of lithium aluminum hydride reduction of the acetals and ketals in the presence of a Lewis acid.

LITERATURE SURVEY

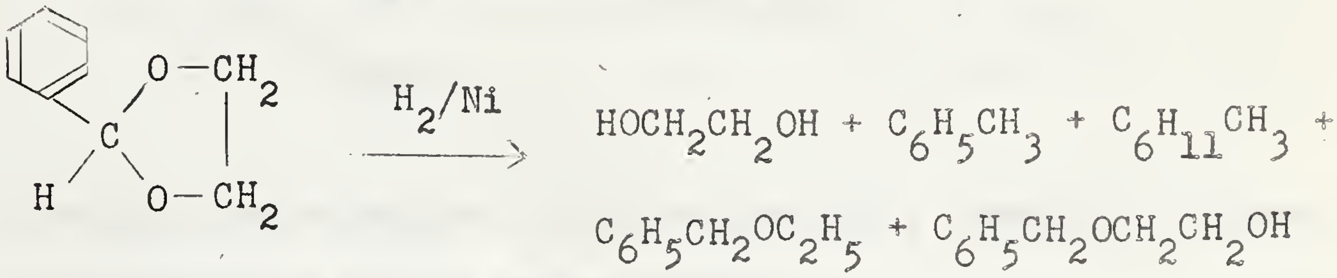
The reduction of acetals and ketals has been reported in the literature by several workers. Prior to 1951, when Doukas and Fontaine (1) discovered that ketals may be reductively cleaved by a combination of lithium aluminum hydride and a hydrogen halide, the pertinent literature dealt with the use of less selective reducing

agents to effect the reduction of acetals and ketals.

Covert, Connor and Adkins (2) reported the reduction of several acetals and ketals by hydrogenation over a nickel catalyst. These workers found, in the majority of cases, that complete reduction of the acetal group occurred. The aldehyde or ketone was converted to a hydrocarbon, and the alcohol was regenerated as shown below.

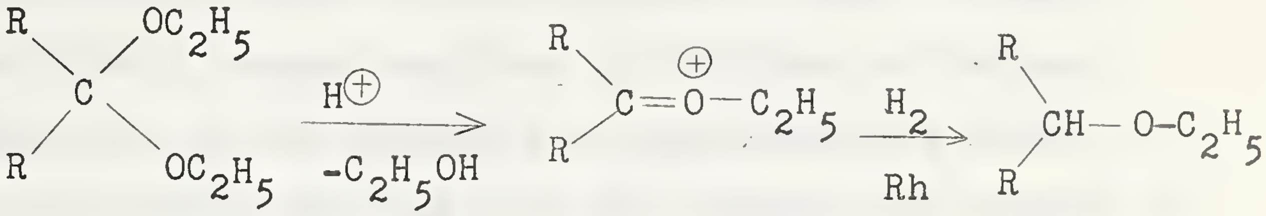

R
R'
C
O-CH2
O-CH2
H2/Ni
R
R'
CH2 + HOCH2CH2OH

However, in a few instances, products resulting from the cleavage of only one of the carbon-oxygen bonds were obtained. For example, the reduction of 2-phenyl-1,3-dioxolane afforded a mixture consisting of ethylene glycol (53%), toluene and methylcyclohexane (41%), benzylethyl ether (12%) and 2-benzyloxyethanol (21%).

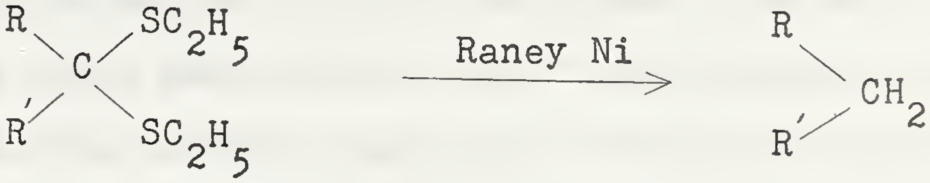

C
H
O—CH2
O—CH2
H2/Ni
HOCH2CH2OH + C6H5CH3 + C6H11CH3 +
C6H5CH2OC2H5 + C6H5CH2OCH2CH2OH

Marker and Rohrmann (3) also found that catalytic hydrogenation of ketals afforded undesirable side products. However Howard and Brown (4) found that acetals and ketals may be successfully reduced to ethers by catalytic hydrogenation, in an acidic medium, using a rhodium catalyst.

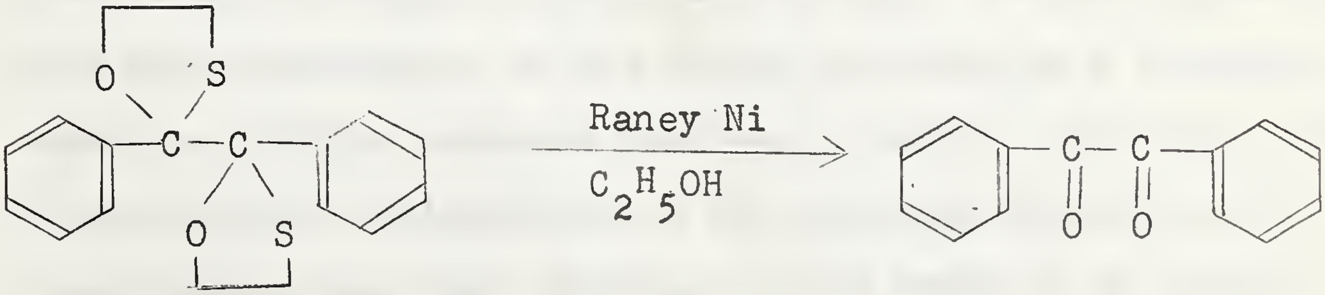
These workers offered a mechanistic scheme for the reduction involving the prior formation of an oxocarbonium ion and its subsequent reduction to yield the ether.



Raney nickel has been used by many workers as a reagent for the reduction and cleavage of mercaptals and hemi-thioacetals and ketals. Amongst the relevant reports in the literature are papers by Fieser (5) and Wolfrom and Karabinos (6) describing the use of Raney nickel to effect the reduction of mercaptals to the corresponding hydrocarbons.



Marshall and Stevenson (7) have used this reagent to cleave hemithioketals to the parent ketone.



Sodium and liquid ammonia has long been employed as a reagent for the cleavage of carbon-oxygen and carbon-sulphur bonds in organic molecules. In 1950 Hughes

and Thompson (8) compared the relative ease of reduction of oxygenated ethers and thioethers by this reagent. They showed that thioethers undergo reductive cleavage with much greater facility than do the oxygenated ethers. Earlier work with this reagent was done by Williams and Gebauer-Fuelnegg (9), on the reduction of carbon-sulphur bonds, and by Santonetto and Sowa (10) who studied the cleavage of oxygenated ethers.

Since the discovery of the reducing powers of the double hydrides, of which the best known and most widely used are lithium alumium hydride and sodium borohydride, the scope of organic reductions has changed appreciably. Many reductions can now be accomplished which, until the advent of the double hydrides, either did not proceed at all or which afforded low yields and many undesirable by-products by older reduction procedures. In the past few years many reviews have been published on the uses of the double hydrides and their versatility as reducing agents. The most comprehensive of these reviews appears to be that of Gaylord (11) whilst that of Eliel (12) gives excellent coverage of the topic as well. The most powerful, and least selective, of the double hydrides as a reducing agent is lithium aluminum hydride. However, in recent years, a much greater selectivity in the reducing properties of this reagent has been obtained by the addition of certain reagents. The most commonly used reagent is apparently aluminum chloride (13) although a wide variety of other

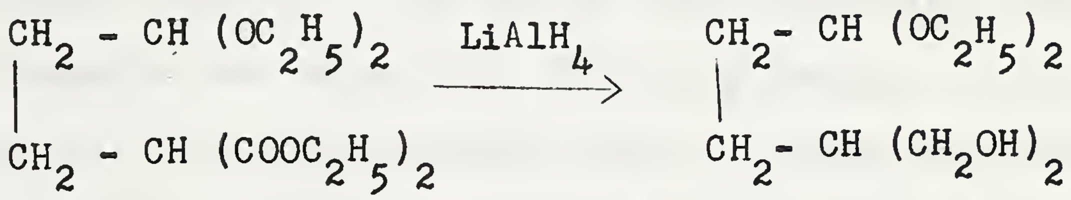
inorganic reagents have also been employed (13).

The combination of lithium aluminum hydride and aluminum chloride gives rise to what is commonly known as a "mixed hydride." The use of this mixed hydride may drastically alter the course of the reduction of organic compounds to afford products different from those obtained by reduction with lithium aluminum hydride alone (13). In certain other cases the use of the mixed hydride is found to bring about reduction whereas no reduction is obtained by the use of lithium aluminum hydride alone. Such a case in point being the hydrogenolysis of acetals, ketals and their sulphur analogues.

The inertness of ethers towards attack by the double hydrides is well known (11), indeed ether solvents such as diethyl ether, tetrahydrofuran and 1,4-dioxane are commonly used in reductions involving the double hydrides. However, certain ethers may be reductively cleaved by mixed hydrides formed by a combination of lithium aluminum hydride with reagents such as aluminum chloride (14) or cobalt chloride (15) although this proceeds with some difficulty.

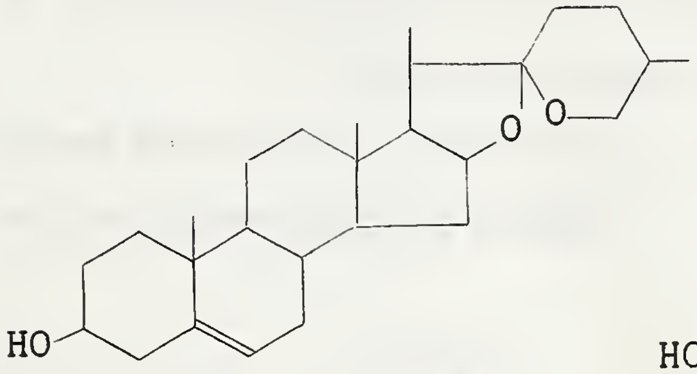
The hydrogenolysis of acetals and ketals may be said to be a special type of ether cleavage. As is generally the case with ethers, no reduction of the carbon-oxygen bond is observed when they are treated with lithium aluminum hydride alone (11). In fact, this inertness of acetals and ketals towards attack by this reagent has long been utilised as a means of protecting carbonyl groups

against reduction whilst other susceptible groups in the molecule are being reduced (11). For example, Marvel and Hill (16) were able to prepare keto alcohols by reduction of the corresponding esters by lithium aluminum hydride after protection of the carbonyl group by the formation of the ethylene ketal as indicated in the following equation.

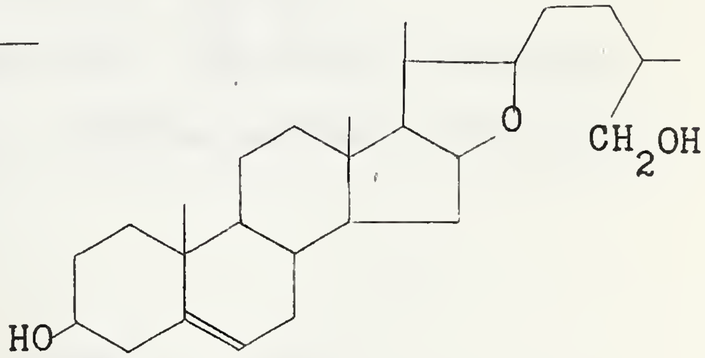


$$\begin{array}{l} \mathrm{CH_2 - CH\,(OC_2H_5)_2} \\ | \\ \mathrm{CH_2 - CH\,(COOC_2H_5)_2} \end{array} \xrightarrow{\mathrm{LiAlH_4}} \begin{array}{l} \mathrm{CH_2 - CH\,(OC_2H_5)_2} \\ | \\ \mathrm{CH_2 - CH\,(CH_2OH)_2} \end{array}$$

In 1951, Doukas and Fontaine (1) observed that the ketal group in diosgenin (K) underwent hydrogenolysis upon treatment with lithium aluminum hydride in the presence of either hydrogen chloride or hydrogen bromide in ether solution, the product of the reduction being dihydrodiosgenin (L).



K.



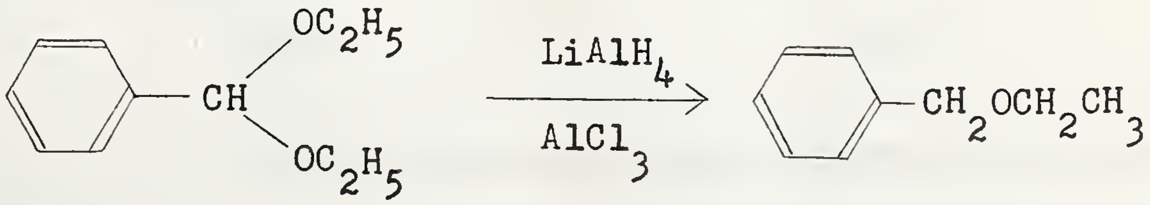
L.

These workers found that although the reduction of diosgenin was promoted by hydrogen halides, various other acidic reagents such as sulphur dioxide, hydrogen sulphide and p-toluenesulphonic acid failed to do so (17).

Since the discovery by Doukas and Fontaine (1)

that ketals may be reduced by lithium aluminum hydride in combination with hydrogen halides, several other groups of workers have investigated the scope of the reaction. Subsequent to the reports of Doukas and Fontaine (1, 17), Eliel and Rerick (18, 19) examined the reduction of acetals and ketals using a combination of lithium aluminum hydride and aluminum chloride. The use of this particular combination of reagents was adopted by Eliel and Rerick on the assumption that the actual reagent used by Doukas and Fontaine (1,17) had in fact been a mixed hydride formed from a combination of lithium aluminum hydride and an aluminum trihalide. The aluminum trihalide was considered to have been formed by the reaction of lithium aluminum hydride with the hydrogen halide. Support for their assumption was the fact that only hydrogen chloride or hydrogen bromide, and no other acidic reagents (sulphur dioxide, hydrogen sulphide or p-toluenesulphonic acid) led to reduction.

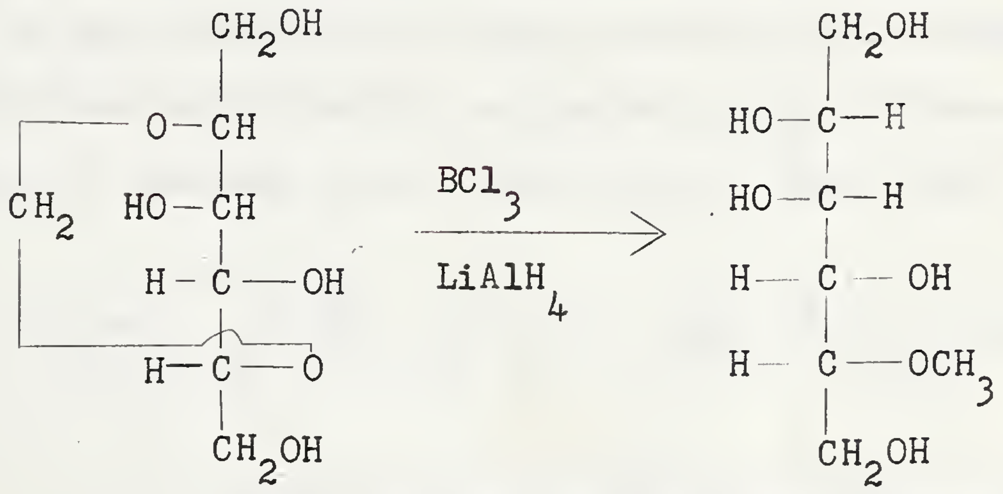
Eliel and Rerick (18, 19) found that this mixed hydride was effective in reducing acetals and ketals to the corresponding ethers.



These authors (19) extended their initial work to include the reductive cleavage of cyclic acetals and ketals.

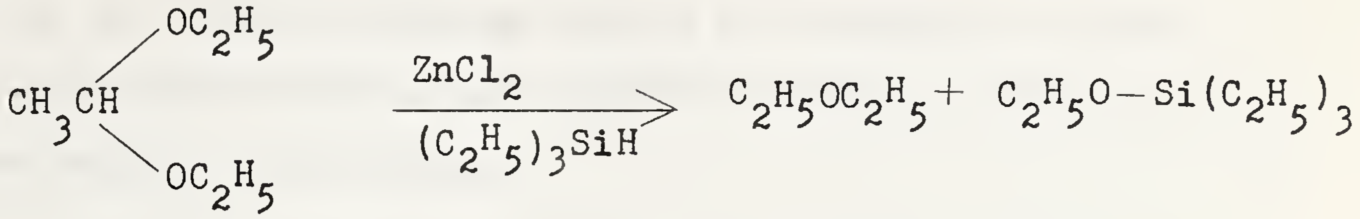
Replacement of the aluminum chloride by boron trifluoride in the mixed hydride has also been found to afford hydrogenolysis of acetals and ketals. Abdun-Nur and Issidorides (20) found that 1,3-dioxanes are reduced, in excellent yield, by a combination of lithium aluminum hydride and boron trifluoride. During the course of their work they observed that formals were reduced at a much slower rate than were the corresponding benzylidene acetals. Eliel, Pilato and Badding (21) have also found that boron trifluoride promotes the reduction of ketals by lithium aluminum hydride.

Bonner and Saville (22) have successfully reduced cyclic acetals of mannitol by the use of a combination of lithum aluminum hydride and boron trichloride.

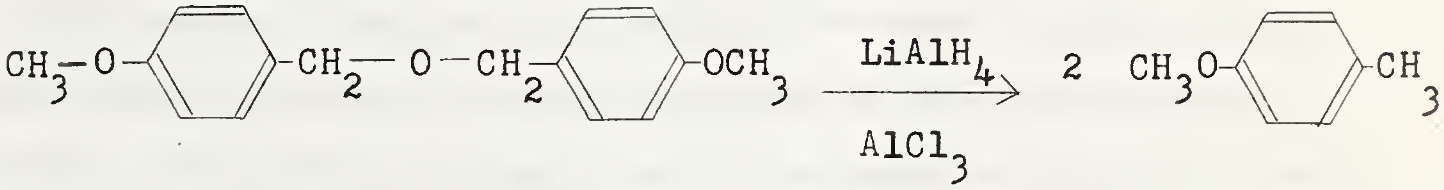


Acetals have also been reduced to the corresponding ethers by the use of a combination of zinc chloride and hydrogenosilanes. Frainnet, Calas and Bazouin (23) investigated this reaction more in an attempt to obtain alkoxysilanes rather than as an investigation into the

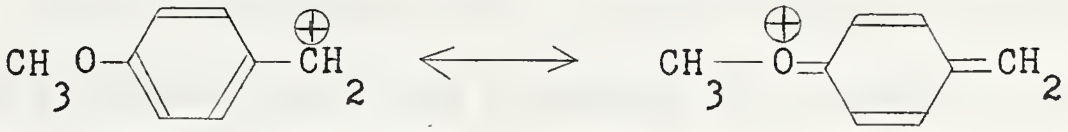
reductive cleavage of acetals.



As mentioned previously in certain cases ordinary ethers themselves may be reductively cleaved by a combination of lithium aluminum hydride and aluminum chloride. Brown and Somerfield (14) successfully reduced benzyl ethers and flavones.

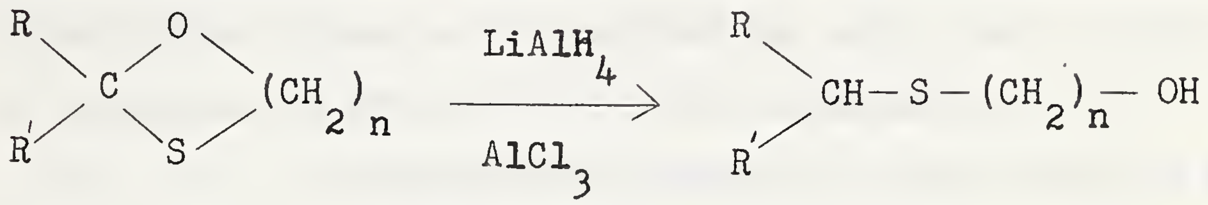


For reduction to proceed, Brown and Somerfield (14) found that it was essential to have present in the phenyl ring groups that could stabilise the incipient carbonium ion formed by cleavage of the ether by the Lewis Acid, e.g.



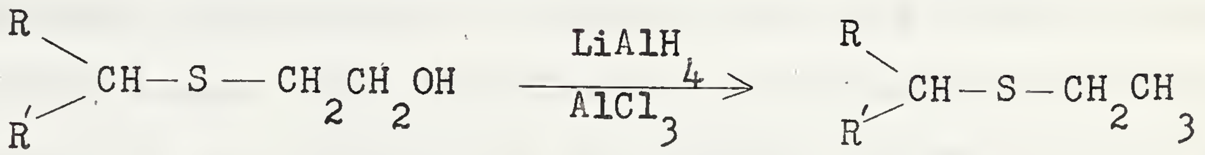
The hydrogenolysis of hemithioacetals and mercaptals by mixed hydrides has been investigated to a far lesser extent by previous workers than has the reductive cleavage of acetals and ketals. The only reports on this subject appearing in the literature are those of Eliel and co-workers (21, 24) who have successfully reduced a number

of cyclic hemithioacetals and hemithioketals with a combination of lithium aluminum hydride and aluminum chloride. They found that in every instance cleavage of only the carbon-oxygen bond occurred.

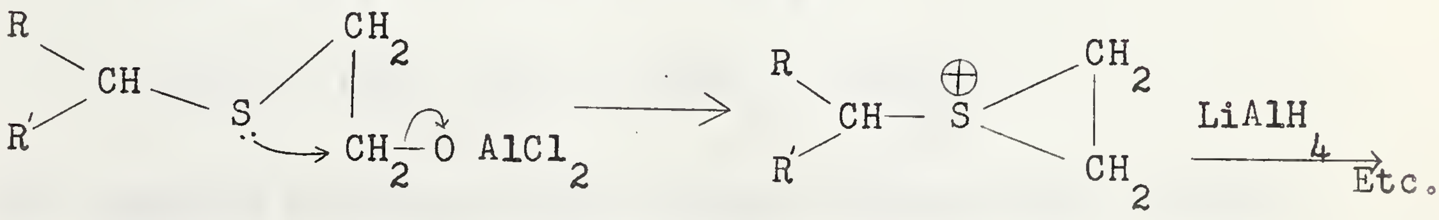


(where n = 2 or 3: R and R′ may be H-, alkyl- or aryl-)

No products corresponding to the reductive cleavage of the carbon-sulphur bond were isolated. Extended reaction times were found to yield further reduction of the hydroxythio ether, the initial product, to the corresponding dialkyl sulphide.



Eliel, Pilato and Badding (21) reported evidence to show that this further reduction proceeded via a cyclic sulphonium ion.



Attempts by the same authors (21) to reduce

a 1,3- oxathiolane with a combination of lithium aluminum hydride and boron trifluoride were unsuccessful, resulting in practically the complete reoovery of the hemithioketal.

There are no reports, in the literature, of the hydrogenolysis of mercaptals by lithium aluminum hydride either alone or in combination with other reagents such as aluminum chloride or the boron trihalides.

A considerable amount of work has been done by various workers in an effort to determine the constitution of the mixed hydride formed when lithium aluminum hydride and aluminum chloride are combined. In the early 1950's Wiberg and co-workers (25, 26) used an equimolar mixture of lithium aluminum hydride and aluminum chloride to effect the reduction of a wide variety of organic compounds. They found that this mixed hydride reagent offered a greater selectivity in reduction than did lithium aluminum hydride alone. The constitution of this mixed hydride was assumed to be a mixture of the aluminum chlorohydrides produced by the following sequence of reactions.

$$3\ LiAlH_4 + AlCl_3 \longrightarrow Al(AlH_4)_3 + 3LiCl$$

$$x\ Al(AlH_4)_3 \longrightarrow 4\ (AlH_3)_x$$

$$AlH_3 + AlCl_3 \rightleftharpoons AlHCl_2 + AlH_2Cl$$

The reducing ability of this reagent has also been studied by Bergerand Nystrom (27).

Mixed hydrides containing aluminum chloride in a greater than equimolar ratio with lithium aluminum hydride have been used as reducing agents by numerous workers (12, 13). The use of excess aluminum chloride may result in a reducing reagent containing both aluminum dichlorohydride and aluminum chloride.

Eliel (12) has stated that "the addition of a Lewis acid weakens the nucleophilic character of lithium aluminum hydride while it simultaneously increases the electrophilic properties of the reagent, such that the overall effect is usually one of producing lowered reducing power."

Evans and co-workers (28, 29) have carried out conductance measurements upon a lithium aluminum hydride aluminum chloride system. Their results indicated that ionic species such as $Al_2Cl_5^{\oplus}$ and $AlH_4^{\ominus}$ may be present in the mixed hydride.

RESULTS AND DISCUSSION

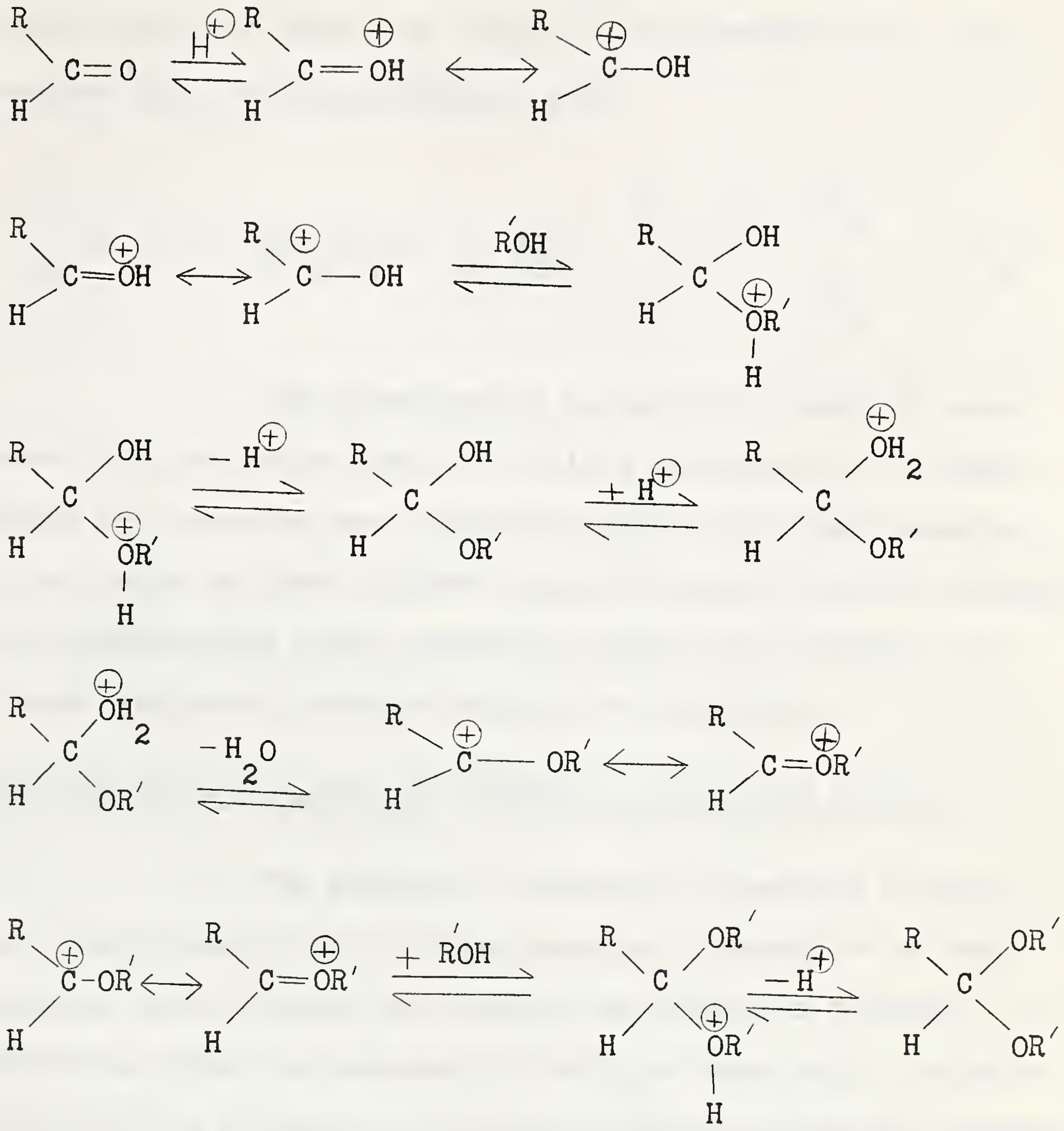
For reasons of clarity and expediency this discussion is divided into two sections. The first section deals with the reductive cleavage of the cyclic hemithioacetals, hemithioketals and mercaptals. The latter section consists of an attempted rationalisation of the results obtained during the investigation into the hydrogenolysis of asymmetrical acetals and ketals by lithium aluminum hydride in combination with Lewis acids.

PART I The Reductive Cleavage of Hemithio- and Dithio-Acetals and Ketals by Lithium Aluminum Hydride in the Presence of a Lewis acid

General Method of Preparation of Dithio- and Hemithio-Acetals and Ketals.

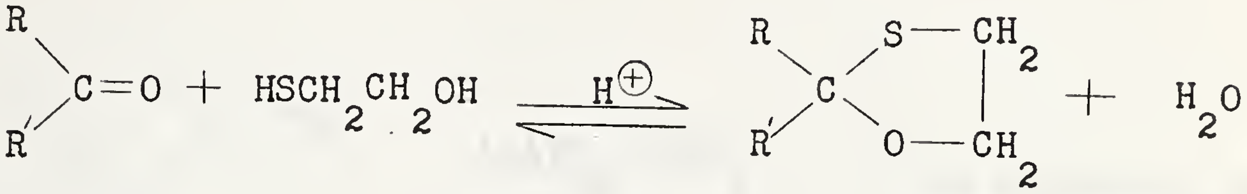
Before proceeding with the discussion of the results obtained from the study of the reductive cleavage of the sulphur acetals and ketals a brief survey of the methods used to synthesise these compounds will be presented.

The preparation of the 1,3-oxathiolanes and 1,3-dithiolanes used in this study was achieved by standard literature methods which involve the acid-catalysed condensation of the carbonyl compound with the particular mercaptan. The recognised pathway for acetal formation is illustrated in the following equations (30).



The preparation of the sulphur acetals from high boiling carbonyl compounds and thiols was most conveniently carried out by condensation in refluxing benzene and toluene since the water formed during the reaction (see following equation) could be removed from the reaction mixture by azeotropic distillation with the solvent (31) via a Dean and Stark (32) water-separator apparatus. The

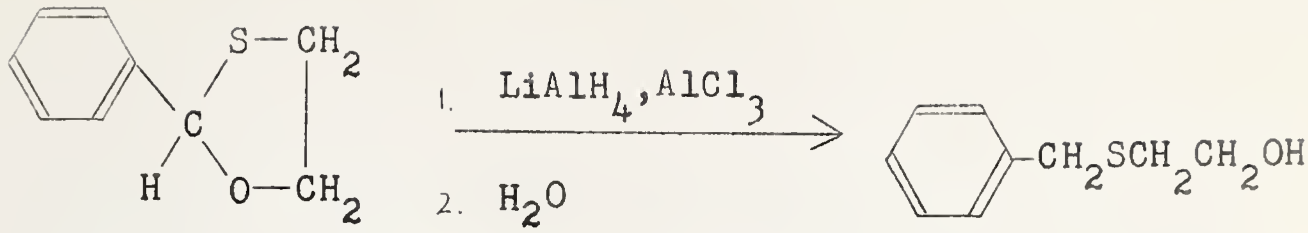
acidic catalyst which was found to be generally most convenient was p-toluenesulphonic acid.



The above method could not be used in cases where the reactants were low boiling substances. In these cases the reaction was allowed to proceed at room temperature, using an inert solvent such as benzene, in the presence of a dehydrating agent, anhydrous magnesium sulphate, to remove the water produced during the reaction.

The Reductive Cleavage of Hemithio Acetals and Ketals

The reductive cleavage of hemithio acetals and hemithioketals by lithium aluminum hydride and a Lewis acid in diethyl ether as solvent, has afforded products resulting from the cleavage of the C_2-O bond only. No evidence of the presence of products resulting from the cleavage of the C_2-S bond was found either in the present study or in the report by Eliel and co-workers (21, 24) of an analogous investigation of the reductive cleavage of sulphur acetals. These reductions are illustrated by the following equations.


S—CH2
C
H
O—CH2
1. LiAlH4,AlCl3
2. H2O
-CH2SCH2CH2OH

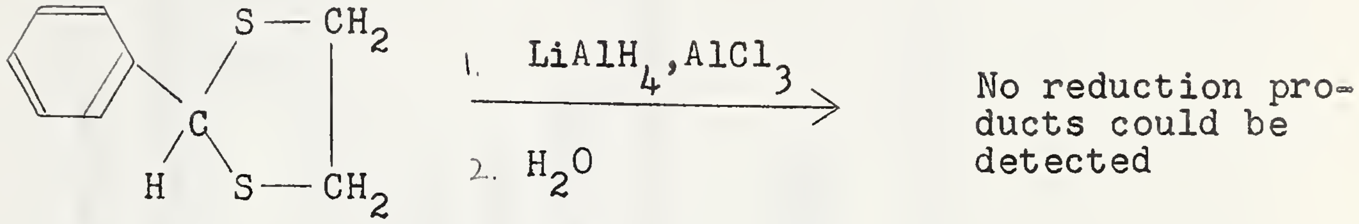

S—CH2
C
H
S—CH2
1. LiAlH4,AlCl3
2. H2O
No reduction products could be detected

Table I, Page 20, gives the results obtained by reduction of hemithioacetals and ketals by lithium aluminum hydride and aluminum chloride in the solvent diethyl ether. Attempts to effect the reductive cleavage of full mercaptals, under the same conditions, proved abortive, only the starting materials being recovered in every case. Table II, Page 21, gives the results of attempted reductions of typical examples of dithioacetals and ketals.

Optimum yields of the reduction products were obtained when the Lewis acid, aluminum chloride, was added dropwise, as a solution in diethyl ether, to a stirred mixture of lithium aluminum hydride and the 1,3-oxathiolane. If the order of addition of the reagents was reversed and the aluminum chloride and hemithioacetal mixed, as a solution in diethyl ether, and then the hydride added, the yield of reduction product was decreased considerably due to the formation of much resinous material.

However when the aluminum chloride was

TABLE I

The Reduction of 1,3-Oxathiolanes by Lithium Aluminum Hydride and Aluminum Chloride

Expt. No.	1,3-Oxathiolane	Reduction Product	% Yield
1.	2-Phenyl-1,3-oxathiolane	Benzyl β-hydroxyethyl sulphide	72
2	2-*n*-Propyl-1,3-oxathiolane	*n*-Butyl β-hydroxyethyl sulphide	89
3	2,2-Dimethyl-1,3-oxathiolane	β-Hydroxyethyl *iso*propyl sulphide	87
4	2,2-Diphenyl-1,3-oxathiolane	Diphenylmethyl β-hydroxyethyl sulphide	73
also			
5	2-Phenyl-1,3-oxathiane	Benzyl γ-hydroxypropyl sulphide	54

TABLE II

1,3-Dithiolanes subjected to Reduction by Lithium Aluminum Hydride and Aluminum Chloride

Expt. No.	1,3-Dithiolane	Recovered Dithiolane, %	Reduction Product, %
1	2,2-Dimethyl-1,3-dithiolane	96	0
2	2,4-Dimethyl-1,3-dithiolane	92	0
3	2-Phenyl-1,3-dithiolane	78	0
4	4-Methyl-2-phenyl-1,3-dithiolane	96	0

replaced by boron trifluoride in combination with the lithium aluminum hydride, the extent of reduction was found to be much more drastically affected by the order of addition of the reagents. Table III, Page 23, illustrates the varying amounts of reduction product obtained by the various procedures used to effect the reductive cleavage of 1,3-oxathiolanes by a combination of lithium aluminum hydride and boron trifluoride. For the sake of convenience these procedures are briefly described here, a much more detailed description of these procedures is to be found in the experimental section.

Method a: The oxathiolane and finely powdered hydride were stirred in diethyl ether while boron trifluoride etherate was added dropwise.

Method b: The oxathiolane and boron trifluoride etherate were mixed in diethyl ether while powdered, lithium aluminum hydride was added.

Method c: The same procedure was employed as for method (b) except that the hydride was added in small lumps.

Method d: The hydride and boron trifluoride were mixed in equimolar quantities in ether and stirred for five minutes prior to the addition of the oxathiolane. During the mixing of the hydride and boron trifluoride a vigorous evolution of gas occurred. Presumably this gas was diborane.

Method (d) is to all intents and purposes the same order of addition of reagents as described in the method used by Eliel and co-workers (21) in their attempted reductions of

TABLE III

The Reduction of 1,3-Oxathiolanes by a Combination of Lithium Aluminum Hydride and Boron Trifluoride

Expt. No.	1,3-Oxathiolane	Method*	Total Recovery %**	Composition of Recovered Material	
				unchanged starting material %	Reduction Product %
1	2,2-Dimethyl-1,3-oxathiolane	a	95	61	39
2	2,2-Dimethyl-1,3-oxathiolane	b	73***	50	50
3	2,2-Dimethyl-1,3-oxathiolane	c	75***	44	56
4	2,2-Dimethyl-1,3-oxathiolane	d	90	>99	<1
5	2-Phenyl-1,3-oxathiolane	c	29***	0	100
6	2-Phenyl-1,3-oxathiolane	a	80	27	73

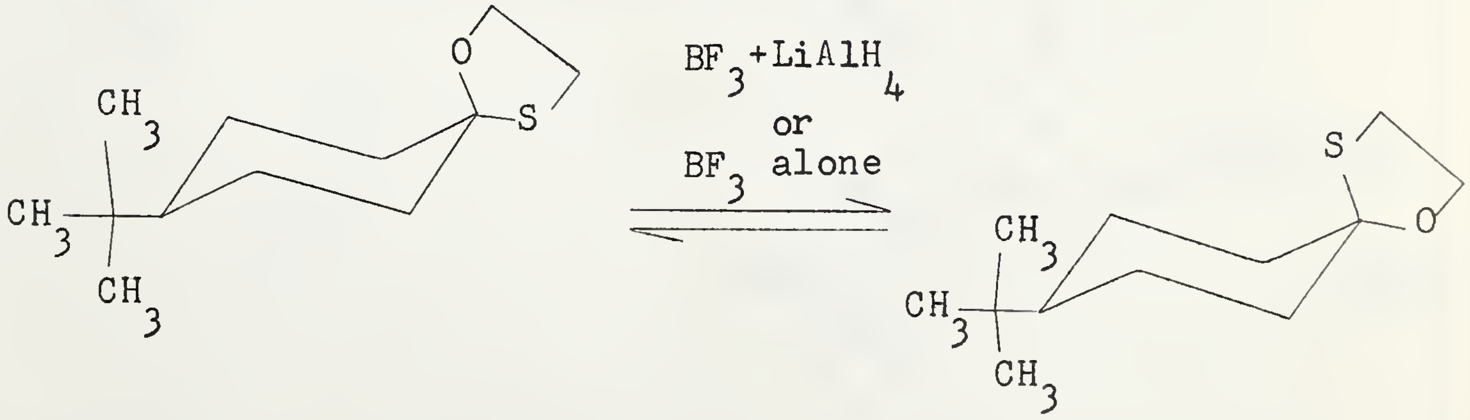
* See Experimental Section for a description of the various methods employed.

** Total Recovery % refers to total material recovered from the reaction.

*** The lower yields were due to the presence of resinous materials in the recovered material.

oxathiolanes by a combination of hydride and boron trifluoride. These workers obtained less than 1% of reduction. product upon the attempted hydrogenolysis of 4-t-butylcyclohexanone ethylene hemithioketal by these reagents. On the basis of this result Eliel and co-workers (21) concluded that a combination of lithium aluminum hydride and boron trifluoride would not effect the reduction of hemithioacetals and ketals and advanced a possible mechanistic scheme based upon this conclusion. The mechanism and reasoning which led to its postulation are briefly outlined in the following paragraphs.

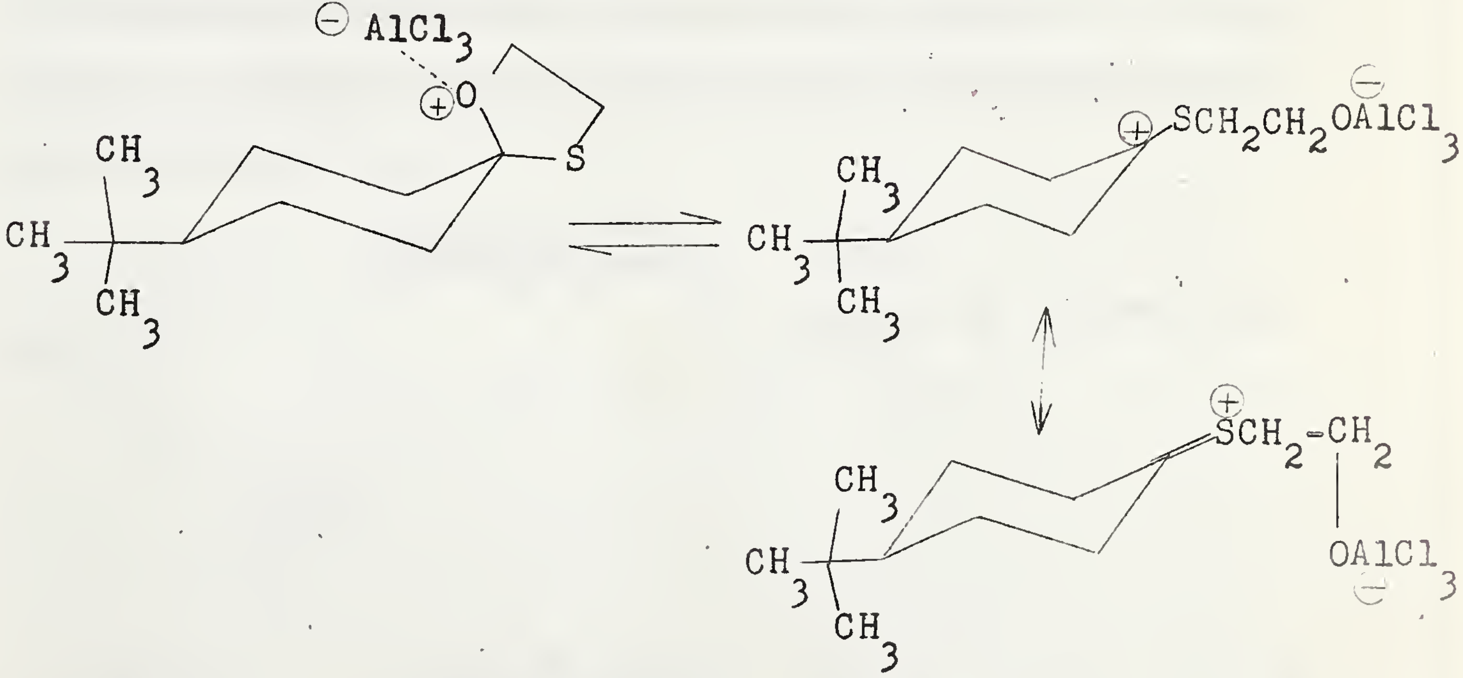
Eliel and co-workers (21) found that although the reduction of 4-t-butylcyclohexanone ethylene hemithioketal, in ether solution, failed to occur with the lithium aluminum hydride-boron trifluoride combination, equilibration of the isomers of this compound did occur readily and cleanly with a 4:1 boron trifluoride to hydride mixture or with boron trifluoride etherate alone. The equilibration of the isomers is illustrated by the following equation.



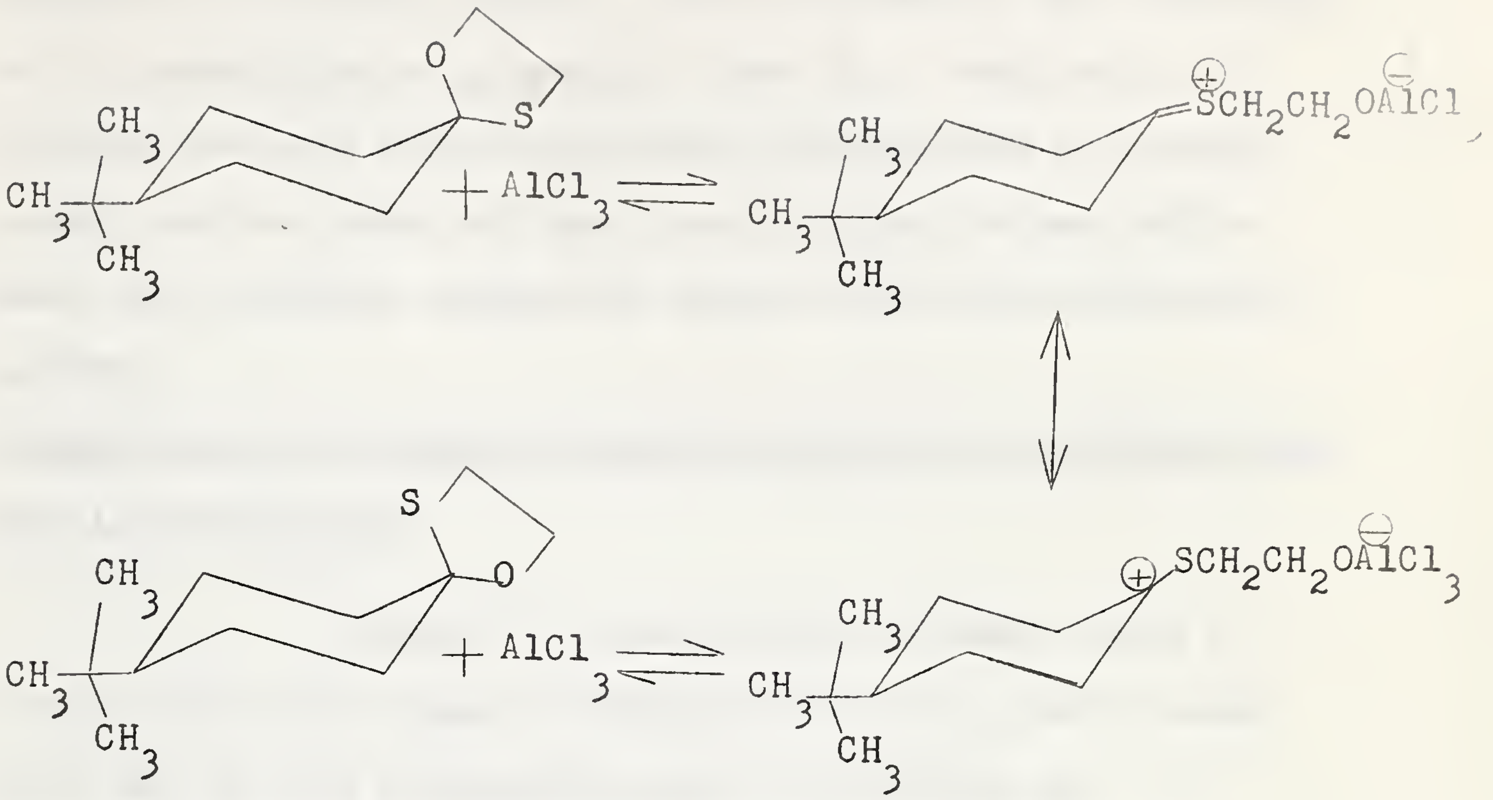
Such isomerisation was also obtained by aluminum chloride in ether solution but accompanied by some decomposition.

On the basis of occurrence of reduction of 1,3-oxathiolanes by a combination of aluminum chloride and lithium aluminum hydride, but the absence of reduction when a combination of boron trifluoride and lithium aluminum hydride was exployed and also the ready equilibration of the isomers of 4-_t_-butylcyclohexanone ethylene hemithioketal by boron trifluoride in ether solution, Eliel and co-workers (21) proposed mechanistic scheme of which the salient features are:-

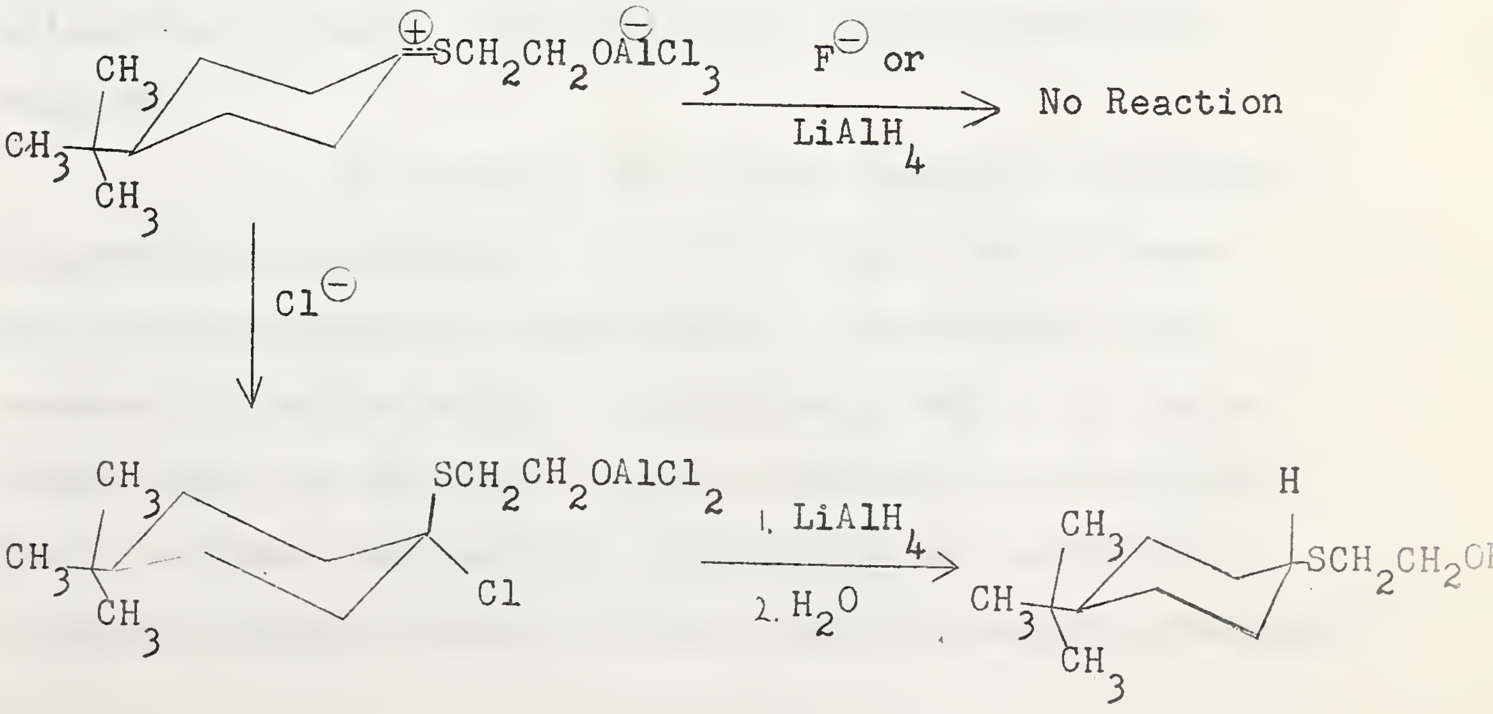
(a) The prior formation of a resonance stabilised sulphocarbonium ion produced by cleavage of the co-ordination complex between the hemithioketal and the Lewis acid as illustrated by the following equation.



(b) This transient sulphocarbonium ion is not reduced by hydride ion directly but does permit equilibration as indicated.


+ AlCl3
SCH2CH2OAlCl3
+ AlCl3
SCH2CH2OAlCl3

(c) Reaction of this sulphocarbonium ion with the more nucleophilic chloride ion from the aluminum chloride but not with the less nucleophilic fluoride ion from the boron trifluoride affords an α-chlorothioether which in turn can easily be reduced by the hydride to the hydroxythioether as illustrated.


SCH2CH2OAlCl3
F⊖ or
LiAlH4
No Reaction
Cl⊖
SCH2CH2OAlCl2
Cl
1. LiAlH4
2. H2O
H
SCH2CH2O

However it is quite apparent from our results that reduction of 1,3-oxathiolanes is brought about by a combination of lithium aluminum hydride and boron trifluoride if certain conditions are observed thus invalidating the main argument used by these workers as support for this mechanistic scheme.

Comparison of the Ease of Hydrogenolysis of 1,3-Oxathiolanes and 1,3-Dioxolanes

During the course of the present study a comparison of the ease of reduction of the 1,3-dioxolanes with that of the 1,3-oxathiolanes was carried out. A number of reductions were performed with 2-n-propyl-1,3-oxathiolane and the corresponding oxygen analogue, 2-n-propyl-1,3-dioxolane, using a combination of lithium aluminum hydride and aluminum chloride as reducing agent. Equimolar proportions of all of the reagents were employed and the reaction conditions were identical in all cases except for the varying lengths of time that each experiment was allowed to proceed. The results are shown in Table IV, Page 28.

It is clear that under identical conditions 2-n-propyl-1,3-dioxolane is reduced considerably faster than is 2-n-propyl-1,3-oxathiolane. The dioxolane was completely reduced within twenty minutes and it is quite likely that the time for complete reduction is less than this. On the other hand the oxathiolane was only half reduced in twenty minutes and the time for complete reduction

TABLE IV

Comparison of the Ease of Reduction of 2-*n*-Propyl-1,3-dioxolane and 2-*n*-Propyl-1,3-oxathiolane by Lithium Aluminum Hydride in the presence of Aluminum Cloride [a]

Expt. No	Total Reaction Time, minutes	Total Recovery [b] %	Yield of Reduction Product %	Amount of recovered starting material %
		For 2-*n*-Propyl-1,3-oxathiolane		
1	20	89	51	49
2	40	84	81	19
3	60	91	91	9
4	210	80	>99.8	<0.2
		For 2-*n*-Propyl-1,3-dioxolane		
5	20	88	100	0

[a] Diethylether was used as solvent.

[b] Total recovery includes the unchanged acetal *and* the reduction product.

was of the order of 210 minutes.

Mechanistic Interpretation of the Results

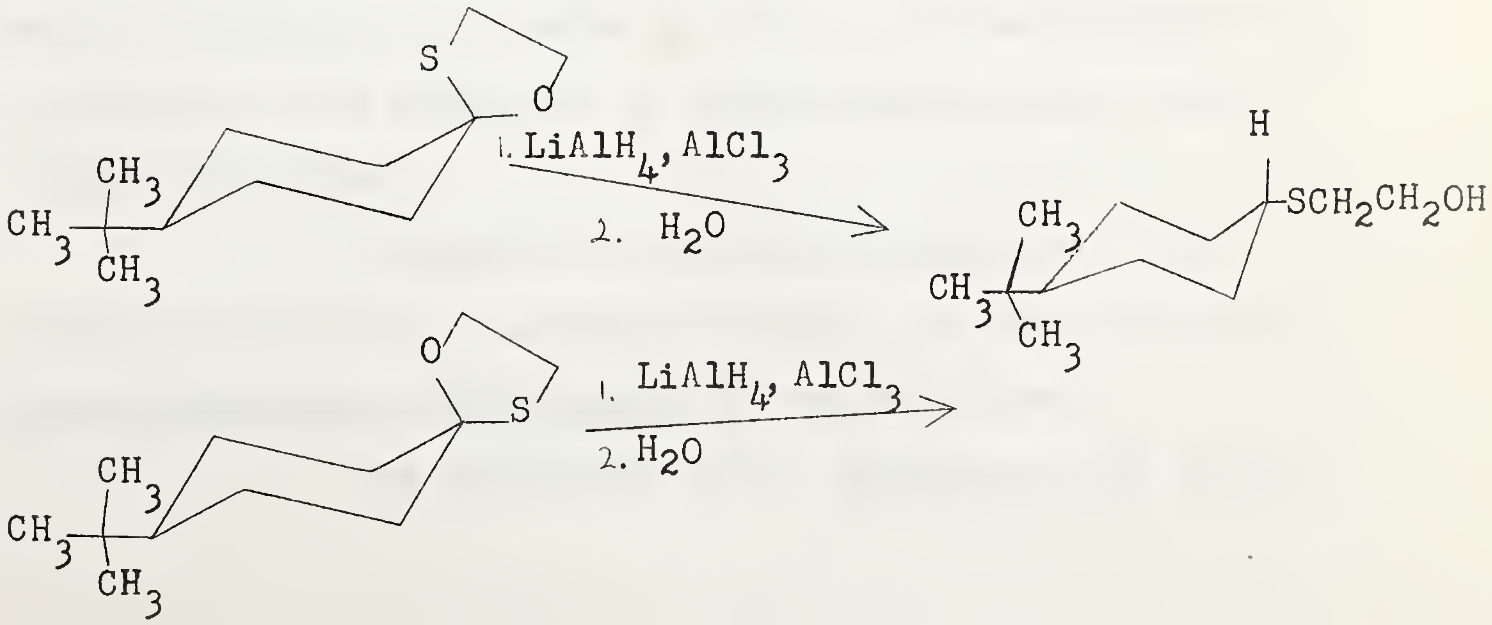
Any mechanistic scheme that explains the reductive cleavage, in diethyl ether solution, of the hemithioacetals and ketals by lithium aluminum hydride in the presence of a Lewis acid must take into account the experimental results described in the preceeding pages of this discussion. The most important features of these results are:-

1) The cleavage of the C_2-O bond but not of the C_2-S bond.

2) The slower rate of reduction of 1,3-oxathiolanes as compared to that of the 1,3-dioxolanes.

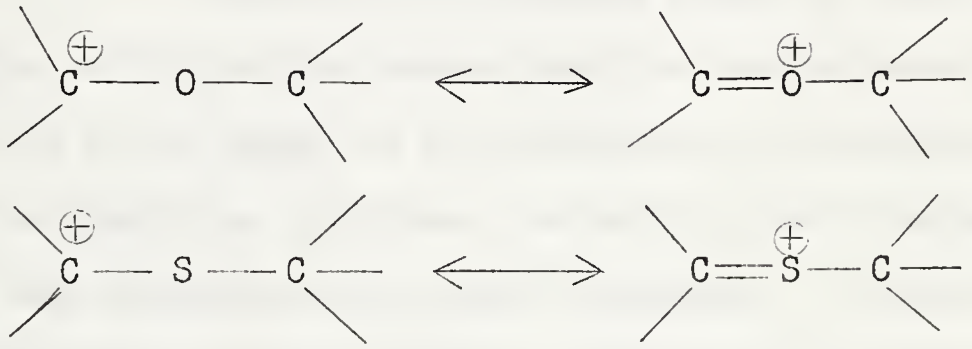
3) The complete failure of 1,3-dithiolanes to be reduced under conditions that result in reduction of 1,3-dioxolanes and 1,3-oxathiolanes.

4) The observation that the reductive cleavage of both of the isomers of 4-t-butylcyclohexanone ethylenehemithioketal affords only the trans isomer of 4-t-butylcyclohexyl β-hydroxyethyl sulphide (21)



5) The variable results obtained when boron trifluoride was used to promote the reduction of 1,3-oxathiolanes by lithium aluminum hydride.

The more rapid rate of reduction of the 1,3-dioxolanes over the 1,3-oxathiolanes may be rationalised by the concept of the more facile formation of the resonance-stabilised oxocarbonium ion intermediate compared to that of a resonance-stabilised sulpho-carbonium ion intermediate as indicated below.



Due to the comparable size of the p orbitals of the oxygen and carbon atoms, an overlap of the p orbitals of the oxygen atom, in the dioxolane, with the vacant p orbital of the carbonium ion is much easier to achieve than in the case of the oxathiolanes. In this case the sulphocarbonium ion is resonance-stabilised by overlap of the 3d orbital of the sulphur atom with the vacant p orbital of the carbonium ion, a situation more difficult to achieve than in the case of oxygen and carbon.

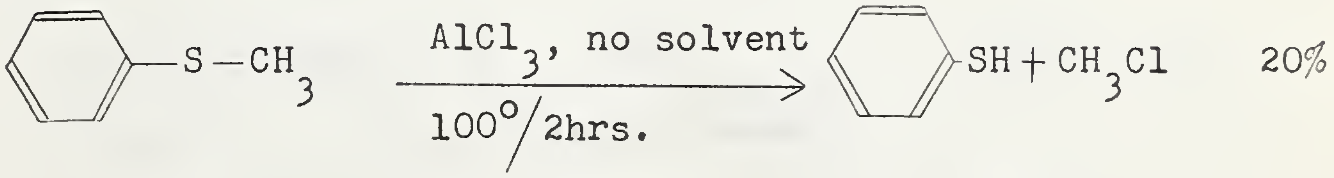
If this is so, then the formation of the resonance stabilised carbonium ion must be involved in the rate controlling step or steps of the reduction.

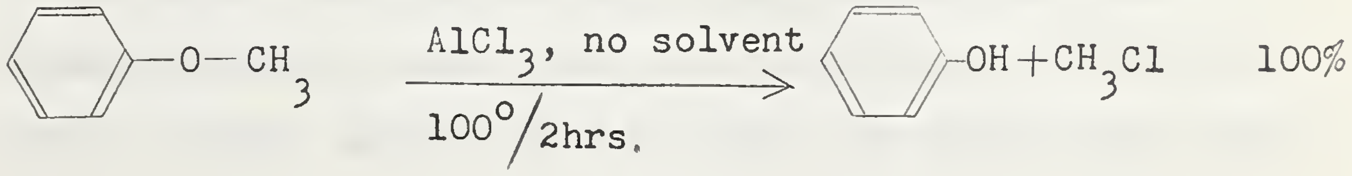
The next point to be discussed will be the

reasons why only the carbon-oxygen bond was cleaned during the reduction of 1,3-oxathiolanes and why no reductive cleavage of 1,3-dithiolanes occurred under the conditions used during the investigation.

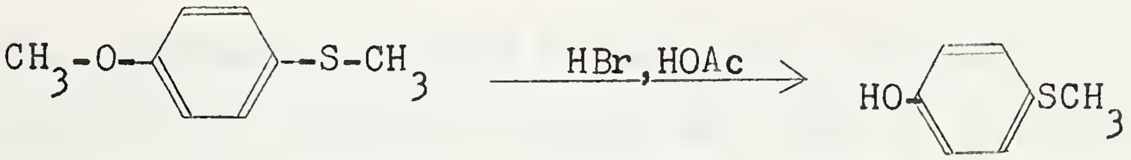
As mentioned previously in this discussion, no evidence of the presence of products resulting from the cleavage of the carbon-sulphur bond was found either in the reduction of 1,3-oxathiolanes or in the attempted reduction of 1,3-dithiolanes.

Although no previous study of the preferential cleavage of the carbon-oxygen bond in hemithioacetals and ketals is to be found in the literature, a considerable amount of work has been done concerning the cleavage of ethers and thioethers by acidic reagents. A comparison of the rates of cleavage of these compounds is reviewed by Tarbell and Harnish (33). Amongst the more pertinent papers to be found in the literature is that of Hughes and Thompson (8). These workers found that thioethers are much more resistant to cleavage by acidic reagents than are their oxygen analogues. However thioethers may be cleaved under forcing conditions as illustrated by the following example.

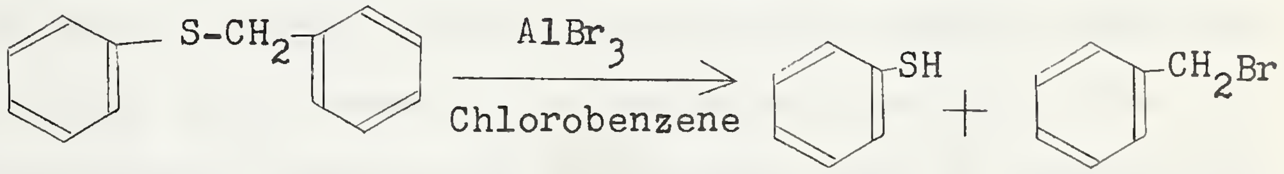


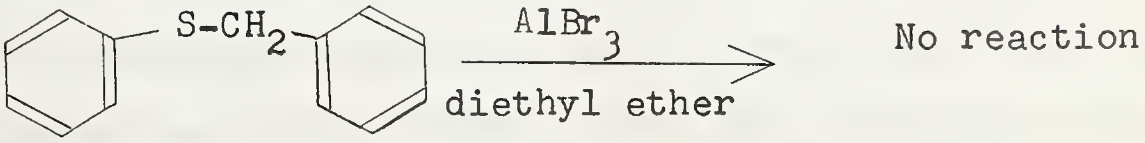


Suter and Hanson (34) found that an acetic acid solution of hydrogen bromide cleaved only the carbon-oxygen bond of p-methoxythioanisole, the carbon-sulphur bond being unattacked by this reagent.



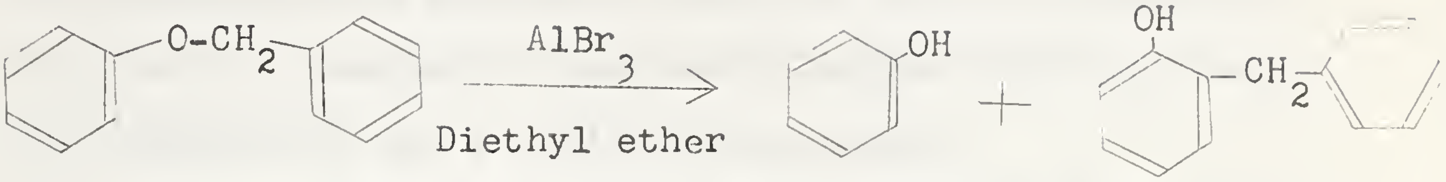
Furthermore in their investigation of the cleavage of benzylphenylsulphide by acidic reagents such as aluminum bromide, Harnish and Tarbell (35) found that the carbon-sulphur bond was cleaved by aluminum bromide when the Lewis acid was allowed to react with the thioether without a solvent or in solvents such as chlorobenzene. However when electron-donor solvents such as ethers or nitrobenzene were used as diluents for this reaction, then the aluminum bromide did not promote the cleavage of the carbon-sulphur bond. These facts are illustrated by the following equations.





On the other hand the corresponding oxygen ether was readily cleaved, under identical conditions, in electron-donor solvents such as diethyl ether, to afford phenol and

o-benzylphenol.



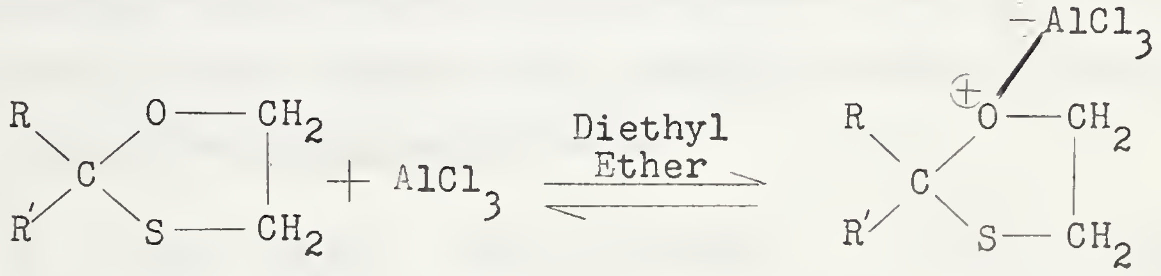
The explanation offered by Harnish and Tarbell (35) to account for the above results was that of preferential co-ordination of the Lewis acid with the electron donor solvents rather than with the sulphur atom of the benzylphenyl sulphide. The benzylphenyl oxyether but not the thioether successfully competed with the solvent for the Lewis acid.

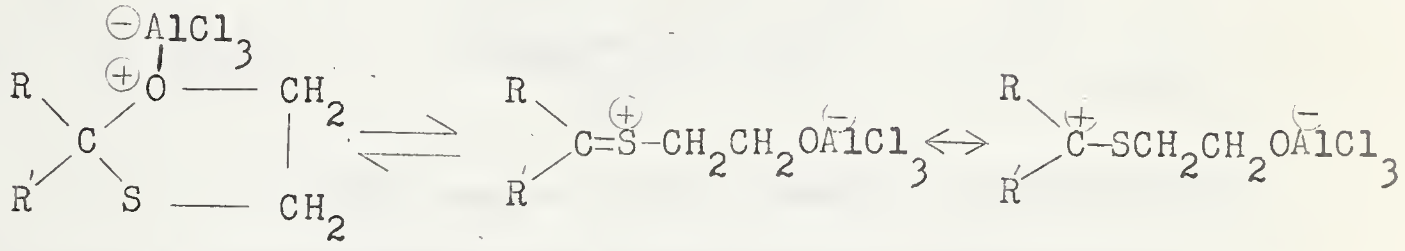
Another illustration of the resistance of the carbon-sulphur bond to attack by acidic reagents is the well-known stability of mercaptals towards hydrolysis by aqueous acids, whereas the corresponding oxygen acetals are easily hydrolysed by acids under similar conditions (33). An explanation similar to that offered by Harnish and Tarbell (35), namely that of preferential co-ordination of the Lewis acid with the oxygen rather than with the sulphur could very well apply in the case of the reductive cleavage of the 1,3-oxathiolanes. Here we are dealing with both an oxygen ether system and a thioether system in the same molecule. As all of the reduction experiments were carried out in the electron-donor solvent , diethyl ether, only the oxygen atom of the oxathiolane would be able to compete effectively with the solvent for the Lewis acid.

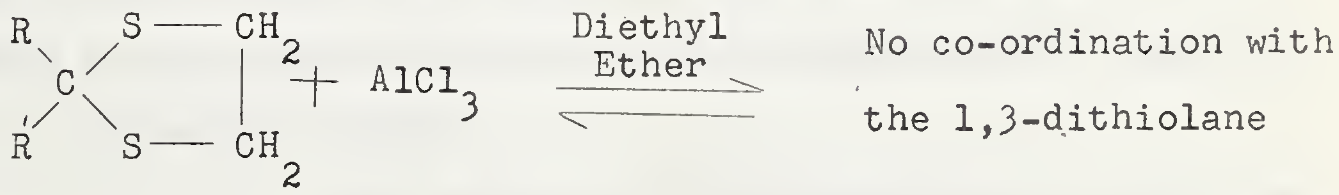
In the case of the attempted reduction of

the 1,3-dithiolanes, the Lewis acid would be preferentially co-ordinated with the solvent molecules rather than with the dithiolane and therefore would not be in a position to catalyse the cleavage of the carbon-sulphur bond and hence the reduction of the 1,3-dithiolane system.

If then, the first and necessary step in the reductive cleavage of the 1,3-oxathiolanes is co-ordination of the oxathiolane with the Lewis acid, then one must have the reaction as shown in the following equation, in which the sulpho-carbonium is formed. This ion could then undergo isomerisation accompanied by some polymerisation or be reduced if lithium aluminum hydride is present.

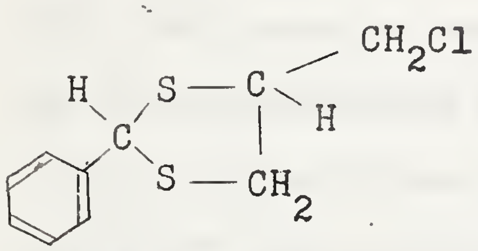

R
R'
O
S
C
CH_2
CH_2
+ $AlCl_3$
Diethyl Ether
$AlCl_3$


$AlCl_3$
R
R'
C
O
S
CH_2
CH_2
$C=S-CH_2CH_2OAlCl_3$
$C-SCH_2CH_2OAlCl_3$

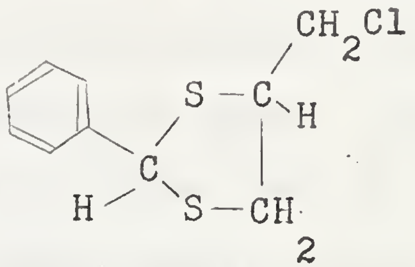

R
R'
C
S
S
CH_2
CH_2
+ $AlCl_3$
Diethyl Ether
No co-ordination with
the 1,3-dithiolane

Support for this concept of the inability of the Lewis acid to associate with the sulphur atom of the 1,3-dithiolanes, in diethyl ether solution, has been gained

by a study of the isomerisation of isomeric dithiolanes by Lewis acids in various solvents. The 1,3-dithiolane used in this study was 4-chloromethyl-2-phenyl-1,3-dithiolane, the cis and trans isomers of which are represented by the following structures.

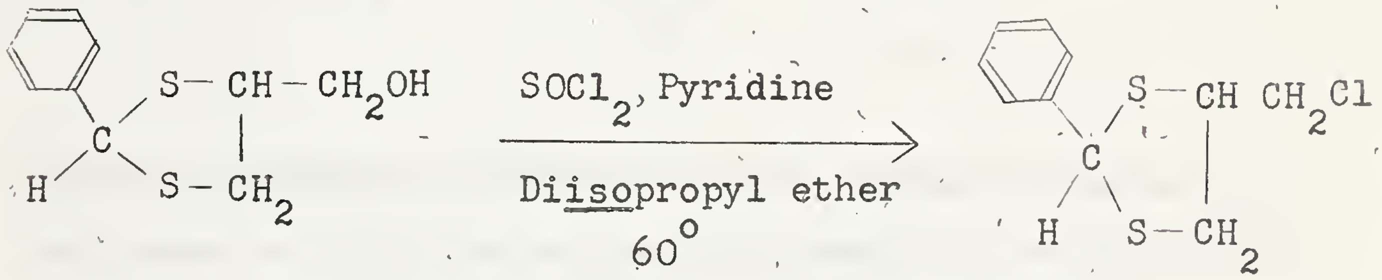


Trans isomer



Cis isomer

The isomers of this dithiolane were conveniently prepared by treatment of the corresponding isomeric 4-hydroxymethyl-2-phenyl-1,3-dithiolanes (36) with thionyl chloride in the presence of a catalytic amount of pyridine in the solvent diisopropyl ether.

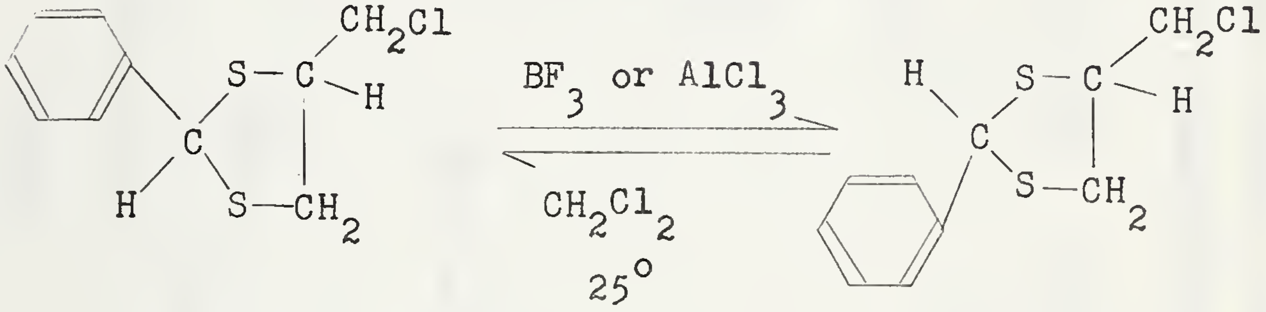


The choice of the isomeric 4-chloromethyl-2-phenyl-1,3-dithiolanes for this study was particularly fortuitous in that both isomers were crystalline solids and their N.M.R. spectra were clearly distinguishable (Figures 1, 2, 3, Pages 37, 38, 39).

For purposes of the isomerisation study the high melting isomer (mp 68-9°) was used as this was found to be the more readily available of the two isomers.

The results of the isomerisation studies of

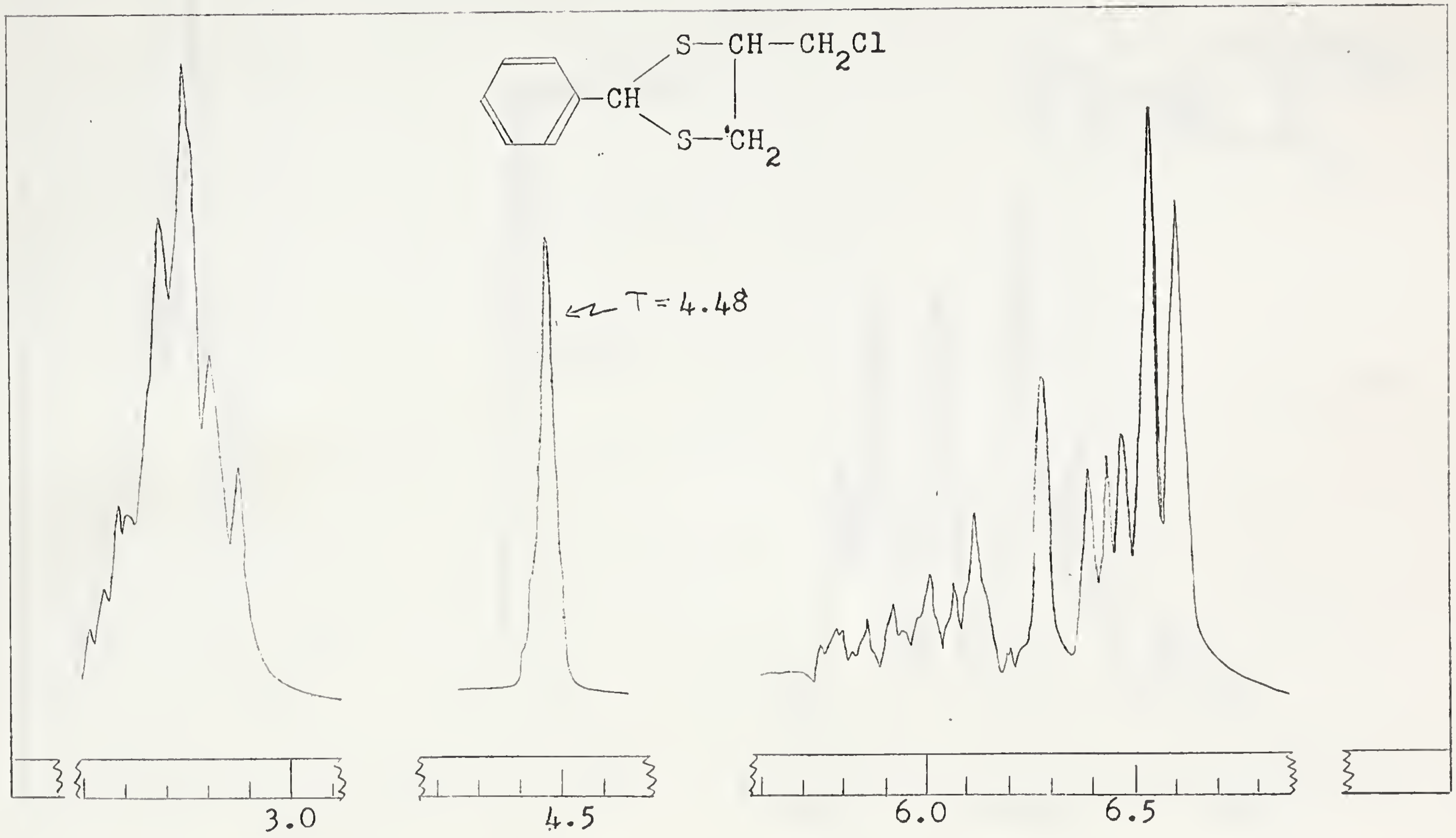
these isomers showed that when diethyl ether was used as the solvent, neither aluminum chloride nor boron trifluoride promoted isomerisation, as inspection of the N.M.R. spectrum of the recovered dithiolane showed. No detectable isomerisation had occurred even when the solution was allowed to stand at room temperature for as long as 20 hours. On the other hand, when methylene chloride, in which both of the Lewis acids and the dithiolane are sufficiently soluble, was used as the solvent isomerisation occurred readily. Boron trifluoride afforded complete isomerisation within 90 minutes.



However, aluminum chloride, besides giving isomerisation was found to yield extensive gum formation, no doubt due to polymerisation.

Detection of the occurrence of isomerisation was easily accomplished by comparison of the N.M.R. spectra of the recovered dithiolanes (Fig.4 Page 40) with those of the respective original isomers used in the experiment and also with that of a previously prepared mixture of the two isomers (Fig. 3 Page 39). The identification of the two isomers was carried out by observation of the signal position for the lone proton on C_2 of the dithiolane which

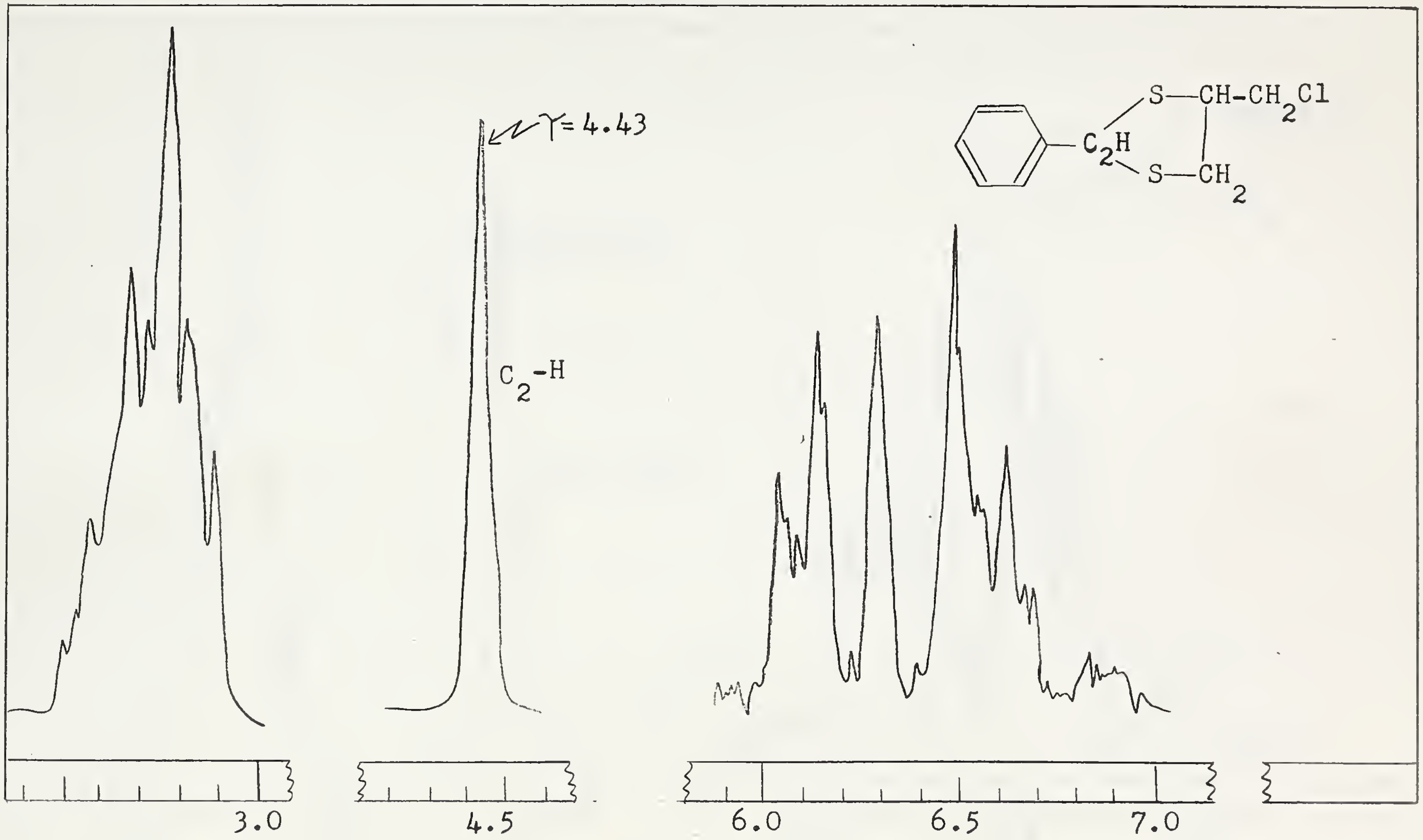
FIGURE I



N.M.R. Spectrum of the low melting isomer (MP 60-62°) of 4-chloromethyl-2-phenyl-1,3-dithiolane (Solvent carbon disulphide).

(referred to tetramethylsilane)

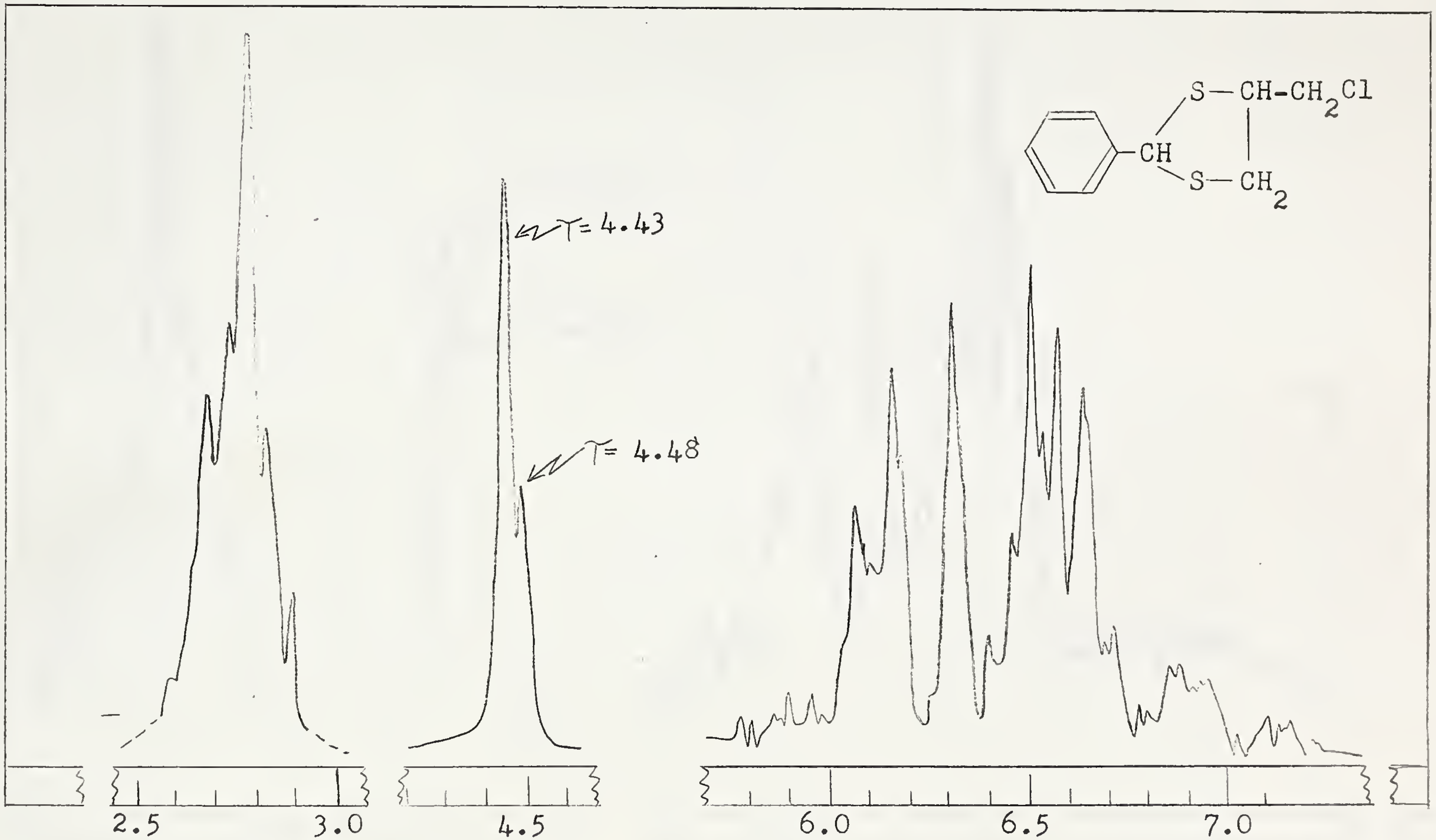
FIGURE 2



N.M.R. Spectrum of high melting isomer (MP. 68-69°) of 4-chloromethyl-2-phenyl-1,3-dithiolane (solvent carbon disulphide)

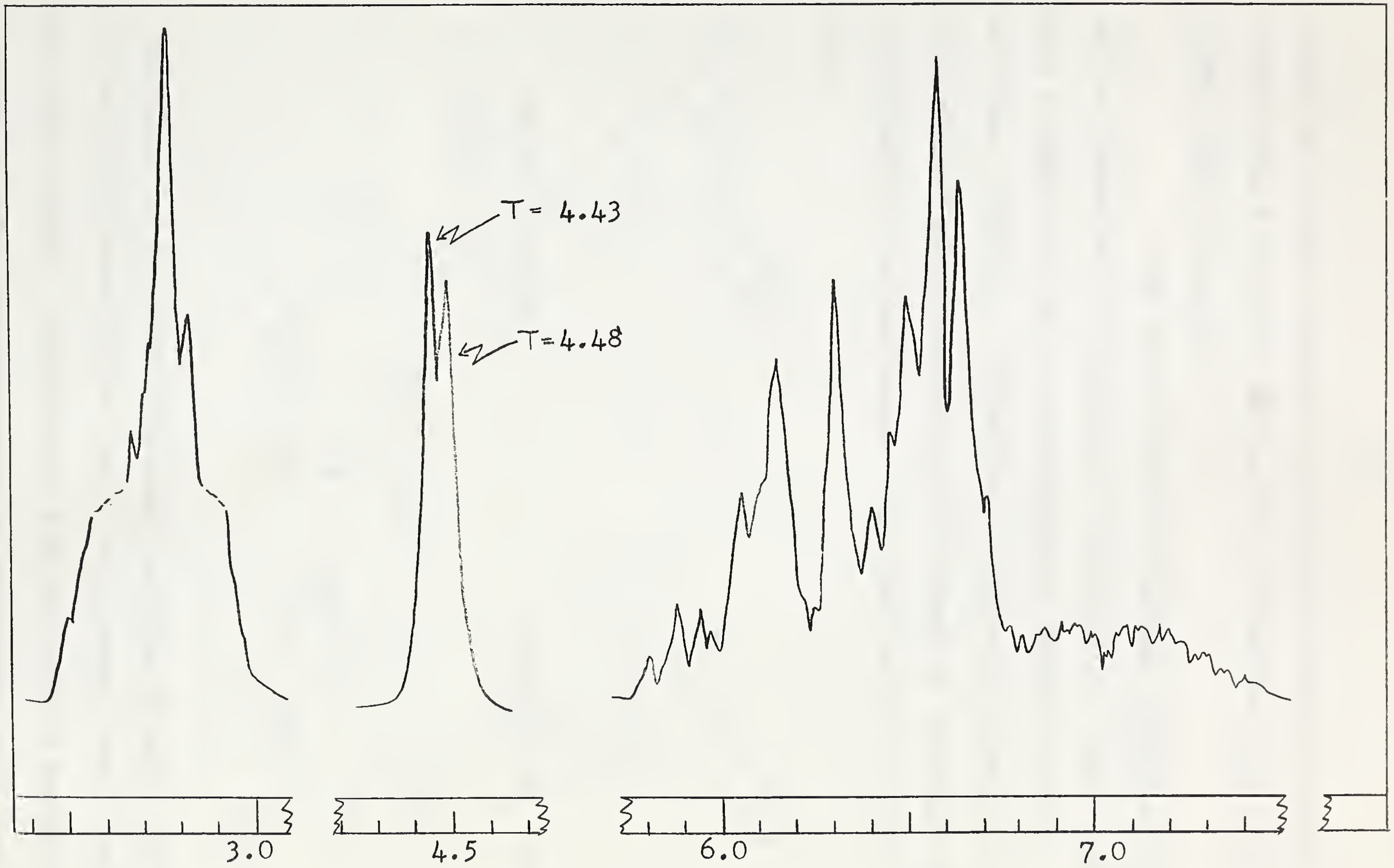
(Referred to tetramethylsilane)

FIGURE 3



N.M.R. Spectrum of an authentic mixture of the high- and low-melting isomers of 4-chloromethyl-4-phenyl-1,3-dithiolane (solvent carbon disulphide) (referred to tetramethylsilane)

FIGURE 4

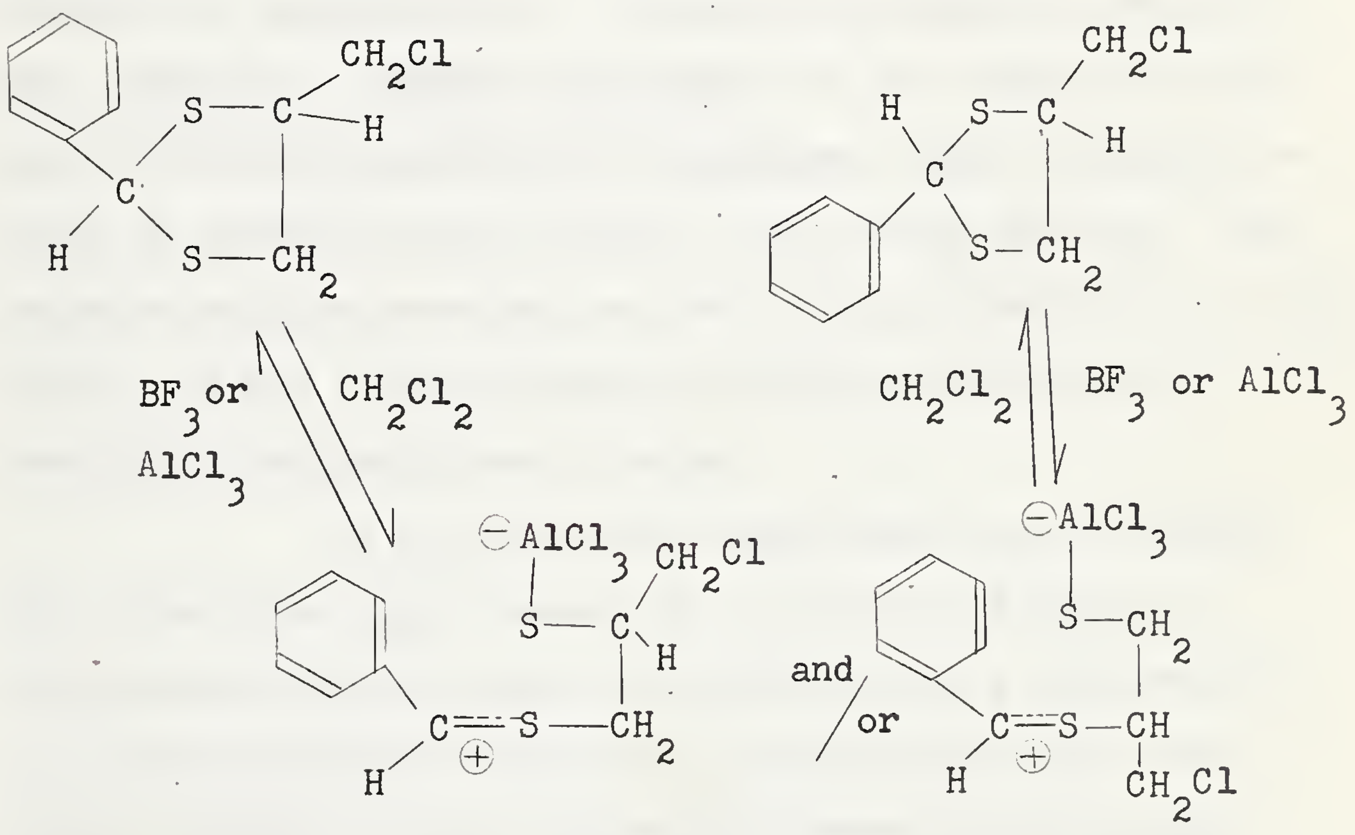


N.M.R. Spectrum of product obtained on treatment of high melting isomer (M.P.68-9°) of 4-chloromethyl-2-phenyl-1,3-dithiolane with boron trifluoride in methylene chloride (solvent carbon disulphide)

(referred to tetramethylsilane)

occurs as a sharp singlet at T=4.48 for the low melting isomer (Fig.1 Page 37) and at T=4.43 for the high melting isomer (Fig.2 Page 38).

The above results show that isomerisation of the isomer of the dithiolane occurred only when treated with a Lewis acid in a non-oxygenated solvent such as methylene chloride. Isomerisation can only occur via an intermediate sulpho-carbonium ion formed by cleavage of the co-ordination complex between the Lewis acid and the dithiolane.

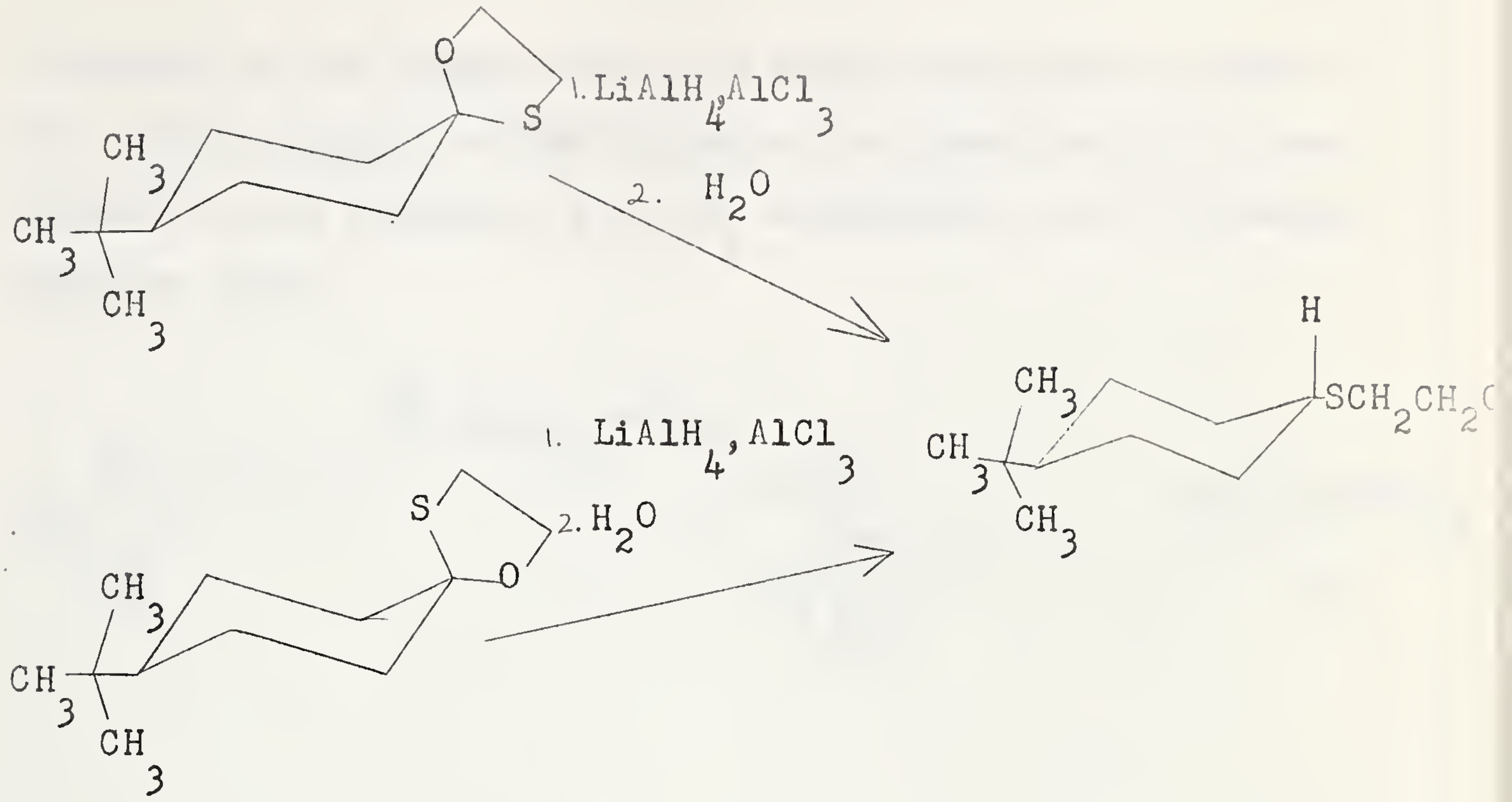

CH2Cl
S
C
H
C
H
S
CH2
BF3 or AlCl3
CH2Cl2
⊖AlCl3
CH2Cl
S
C
H
C
H
⊕
S
CH2
and/or
CH2Cl
H
S
C
H
C
S
CH2
CH2Cl2
BF3 or AlCl3
⊖AlCl3
S
CH2
C
H
⊕
S
CH
CH2Cl

A corollary of the above statement is that if association of the dithiolane with the Lewis acid occurs then isomerisation will result. Therefore we can say that in methylene chloride solvent the dithiolane is associated with the Lewis acid. However in a solvent such as diethyl ether, in which

isomerisation did not occur, the Lewis acid, being preferentially associated with the solvent, is not available to co-ordinate with the dithiolane.

This being the case, then it should be possible to effect the reductive cleavage of 1,3-dithiolanes in non-oxygenated solvents as in these solvents the first and necessary step in the reduction process, the formation of the sulpho-carbonium ion intermediate, is expected to occur. Accordingly such reductions were attempted using aluminum chloride as the Lewis acid in solvents such as methylene chloride or skellysolve B. However no reduction products were obtained. Similar experiments on the reductive cleavage of 2,2,4-trimethyl-1,3,-dioxolane, which is easily reduced in diethyl ether solvent, also proved abortive. The negative results obtained are due in all probability, to the failure of the lithium aluminium hydride to dissolve in skellysolve or methylene chloride.

It is noteworthy that Eliel and co-workers (21) found that both isomers of 4-*t*-butylcyclohexanone ethylenehemithioketal gave, on reduction by a combination of lithium aluminum hydride and aluminum chloride, high yields (86-92%) of the exclusively formed product, *trans* 4-*t*-butylcyclohexyl β-hydroxyethyl sulphide, as indicated by the following equation.

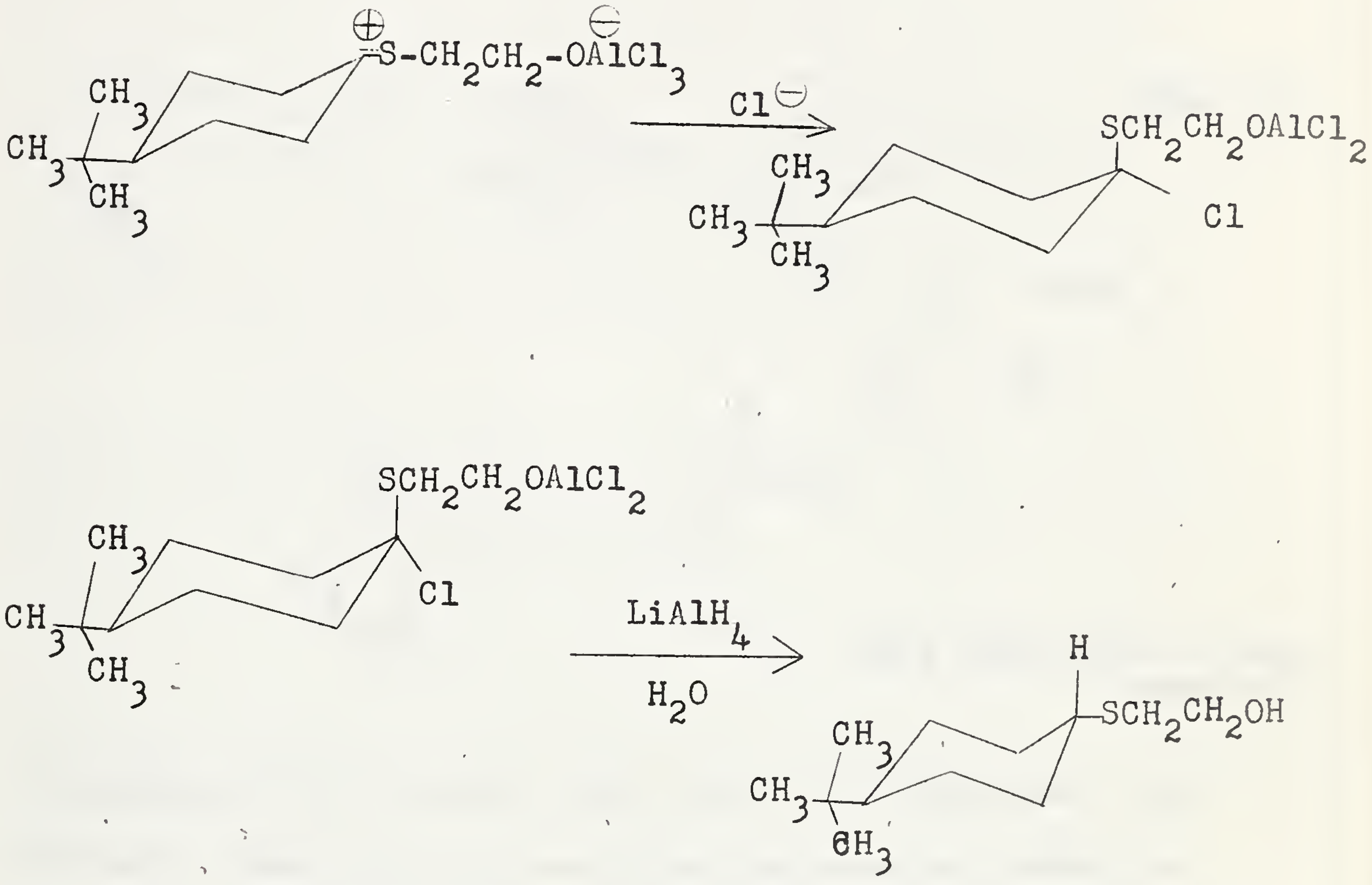


None of the cis isomer was formed.

This seemingly indicates that either the reduction of both isomers proceeds via a common intermediate or that both isomers are rapidly equilibrated with subsequent and quantitative formation of only one of the isomeric α-chlorothioethers, which is then reduced stereospecifically. This latter explanation is of doubtful probability because Eliel and co-workers (21) found that equilibration proceeded slowly, an equilibrium mixture of the isomers (ca 1:1 ratio) being attained only after 24 hours' treatment with boron-trifluoride in diethyl ether solution. Many of our reductions were completed in less than three hours.

Furthermore, the postulation by Eliel et al. (21) that the sulphocarbonium ion cannot be directly reduced by the hydride but must first be converted to the α-chlorothioether is open to criticism. To explain the exclusive

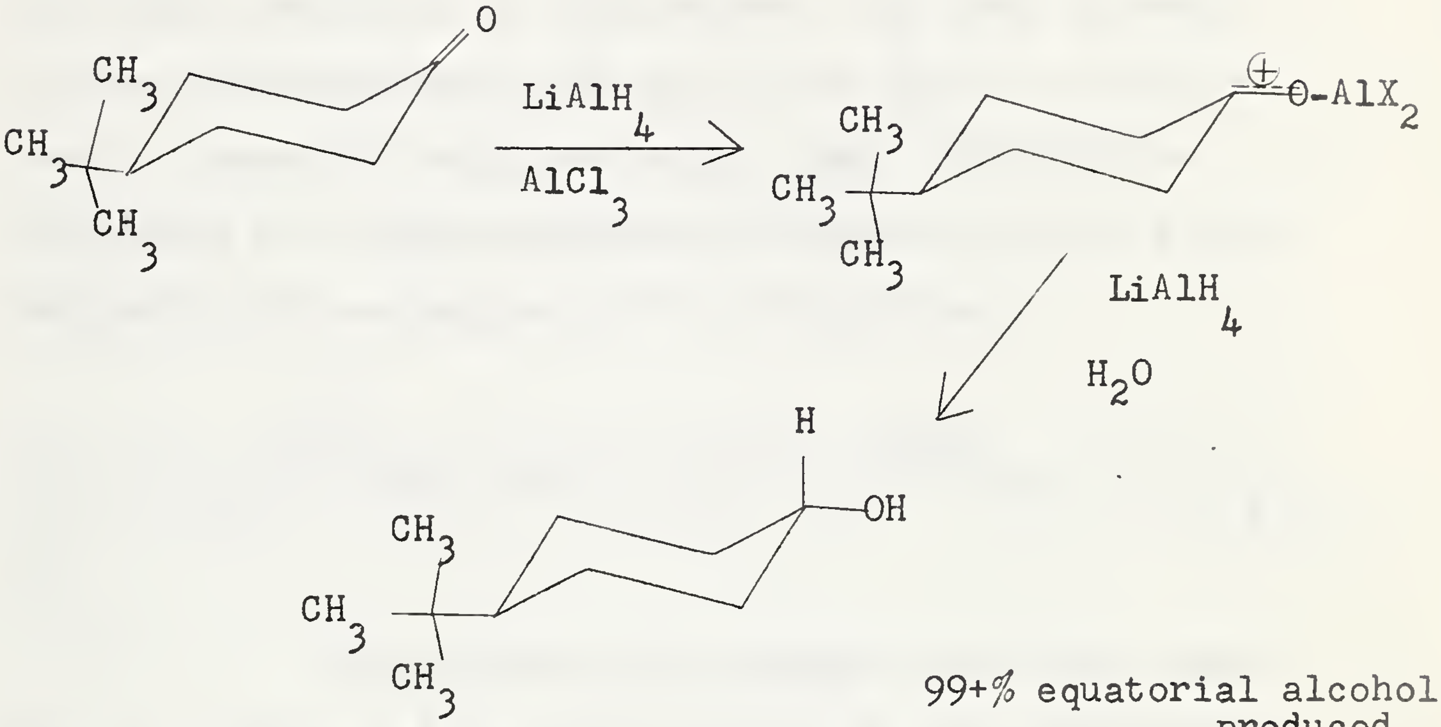
formation of the *trans* product we would then have to assume that only the *cis* α-chlorothioether is formed which is then reduced by the hydride via an SN_2 mechanism as the following equation shows.


CH_3
CH_3
CH_3
$\oplus$
$S-CH_2CH_2-OAlCl_3$
$\ominus$
$Cl^{\ominus}$
$SCH_2CH_2OAlCl_2$
Cl
$SCH_2CH_2OAlCl_2$
Cl
$LiAlH_4$
H_2O
H
SCH_2CH_2OH

This scheme would involve the necessity of the bulky alkoxythio moiety assuming a *pseudo axial* position in the transition state of α-chlorothioether formation.

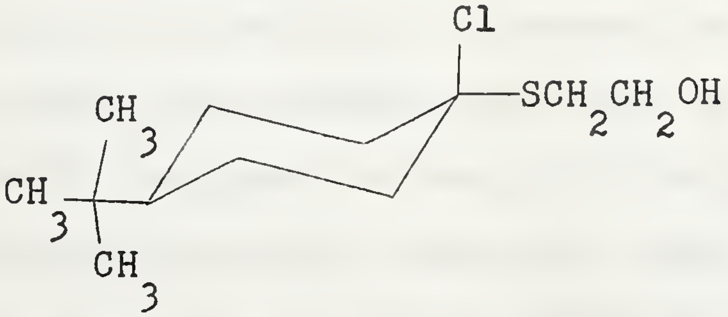
However Wheeler and Mateos (37) and also Eliel (38) have studied the reduction of cyclohexanones by lithium aluminum hydride alone or in combination with aluminum chloride. Their results show that the controlling influence as to whether the *cis* or *trans* alcohols are formed seems to be the preference for the bulky oxygen moiety

to orientate itself into a pseudo equatorial position in the transition stage as illustrated in the following equation.


O
CH3
CH3
CH3
LiAlH4
AlCl3
⊕O-AlX2
LiAlH4
H2O
H
OH

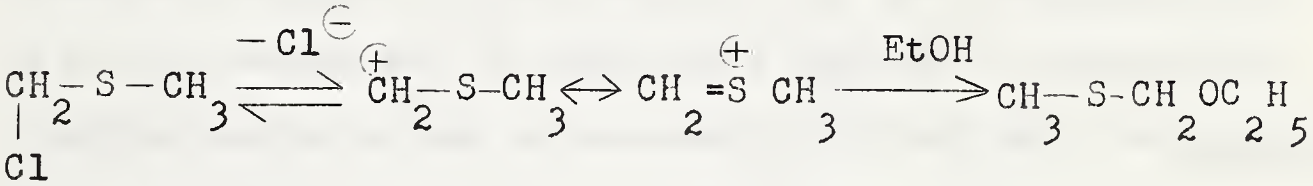
99+% equatorial alcohol produced

Analogously in the present case the α-chlorothioether oontaining an axial chlorine would be the expected product as illustrated.


Cl
SCH2CH2OH
CH3
CH3
CH3

Now, considering the subsequent reduction of the postulated α-chlorothioether intermediate, hydride attack via an SN_2 mechanism would lead to the cis thioether rather

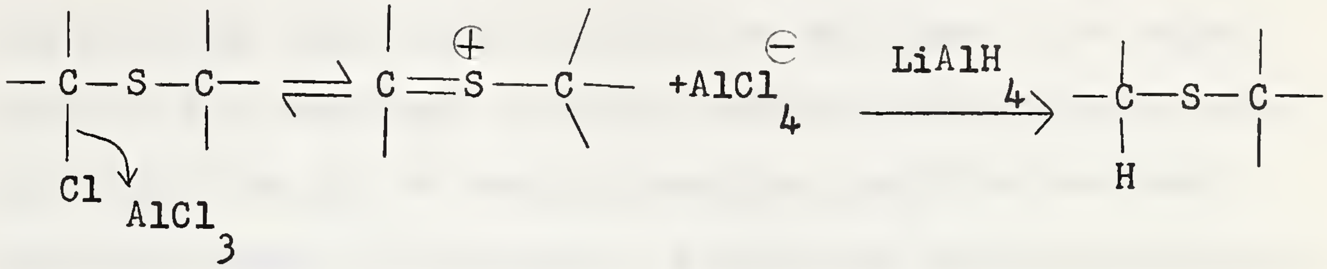
than the trans isomer, the one actually found to be the product. On the other hand if the reduction of α-chlorothioethers proceeds via an SN_1 mechanism which would seem to be more probable in view of the SN_1 character of the solvolysis reactions of α-haloethers (39) then cleavage of the carbon-chlorine bond must occur first to form the readily reducible sulphocarbonium ion. Although the solvolysis of α-halothioethers is known to go via a predominantly SN_1 mechanism (40) as illustrated,



$$\underset{\mathrm{Cl}}{\underset{|}{CH_2}}-S-CH_3 \overset{-Cl^{\ominus}}{\rightleftharpoons} \overset{\oplus}{C}H_2-S-CH_3 \leftrightarrow CH_2=\overset{\oplus}{S}\;CH_3 \xrightarrow{EtOH} CH_3-S-CH_2OC_2H_5$$

De la Mare and co-workers (40) have shown that in solvents of low polarity the SN_2 character of the solvolysis comes more into play but not completely so. These workers confined their investigation to the solvolysis of α-chlorodimethylsulphide in ether-type solvents in the presence of added alkoxide ion and found considerable SN_2 character in the reaction. However, our particular case differs more than somewhat from that of De la Mare et al. Their study involved the reaction of a primary α-halothioether with nucleophilic reagents. Here we are dealing with either secondary or tertiary alkylhalides in the presence of a strong electrophile (aluminum chloride). Under these reaction conditions it appears much more probable that the SN_1 mechanism will prevail over the SN_2 pathway in the

reduction of α-halothioethers.



In view of the fact that sulphocarbonium ion formation is necessary in the isomerisation of oxathiolanes and dithiolanes, in the formation of the preferred α-halothioether and also in the reduction of the α-halothioether by an SN_1 mechanism, it seems more logical to assume that α-chlorination is not a necessary step and that the initially formed sulphocarbonium ion is the species reduced.

Finally the varying results obtained on hydrogenolysis of the 1,3-oxathiolanes with a combination of lithium aluminum hydride and boron trifluoride will be discussed.

As clearly shown in Table III (Page 23), boron trifluoride will catalyse the reductive cleavage of 1,3-oxathiolanes by lithium aluminum hydride contrary to the report of Eliel and co-workers (21). However the yield of reduction products is dependent upon the mode of addition of the reagents and also upon the physical state of the hydride. In the study of the reductive cleavage of dioxolanes and oxathiolanes using aluminum chloride as catalyst it was found that when the Lewis acid is added to an ether solution of the acetal prior to the addition of the hydride,

some resinous material was obtained due, do doubt, to polymerisation of the acetal. The same occurred but to a much lesser extent when boron trifluoride was used. Our experience in the reduction of these acetals and ketals has been that this loss due to resin formation, could be avoided, and good control of reduction, along with quite satisfactory results could be achieved by careful addition of an ether solution of the aluminum chloride to the stirred ether solution of the oxathiolane containing the requisite amount of hydride.

Accordingly this procedure was employed initially in the boron trifluoride-catalysed reduction of the oxathiolanes. It was found that this procedure resulted in only 39% of the total isolated product being the desired hydroxythioether and the remaining 61% being unchanged oxathiolane (Expt. 1, Table III, Page 23). However further investigation showed that if the boron trifluoride and oxathiolane were mixed first and then the hydride added, in a finely divided state, a greater proportion of the product was found to be the reduced material (Expt. 2, Table III). If the previous procedure was used but the hydride added in the form of small lumps (Expt. 3, Table III) an even greater proportion of the product was the hydroxythioether. In both experiments 2 and 3 wherein the boron trifluoride and oxathiolane were first mixed together, somewhat better reduction did occur, though now with resin formation, than by the method of Lewis acid addition to the mixture of hydride and

oxathiolane, the procedure found to be better when aluminum chloride was the Lewis acid used. Finally a repetition of the procedure used by Eliel and co-workers (21) in the attempted reduction of 4-t-butylcyclohexanone ethylene hemithioketal, in which a 4:1 mixture of boron trifluoride etherate and lithium aluminum hydride in ether was stirred for five minutes and to which was then added the oxathiolane, gave less than 1% of the reduction product and 99% of starting material, thus duplicating these authors' results.

It is not surprising that a previously prepared 4:1 mixture of boron trifluoride and hydride in ether failed to effect any reductive cleavage of the oxathiolane. The work of Shapiro et al. (41) on the preparation of diborane indicates that the addition of excess boron trifluoride to lithium aluminum hydride in ether produces diborane and aluminum fluoride according to the overall reaction given by the following equation.

$$3\ LiAlH_4 + 4BF_3 \xrightarrow{Ether} 2\ B_2H_6 + 3LiF + 3AlF_3$$

Because of its low solubility in diethylether, the diborane is evolved (42) and in fact the collection of diborane has been used as a measure of its rate of formation (41) from these reagents. The practically complete loss of the hydride as diborane from the ether solution would thus account for the absence of significant reduction as reported by Eliel et al. (21).

Shapiro and co-workers (41) observed that

no diborane was evolved until the ratio of boron trifluoride added to the lithium aluminum hydride was greater than 1:1, thus indicating a two step sequence shown by the following equations.

$$BF_3 + LiAlH_4 \longrightarrow LiBH_4 + AlF_3\downarrow$$

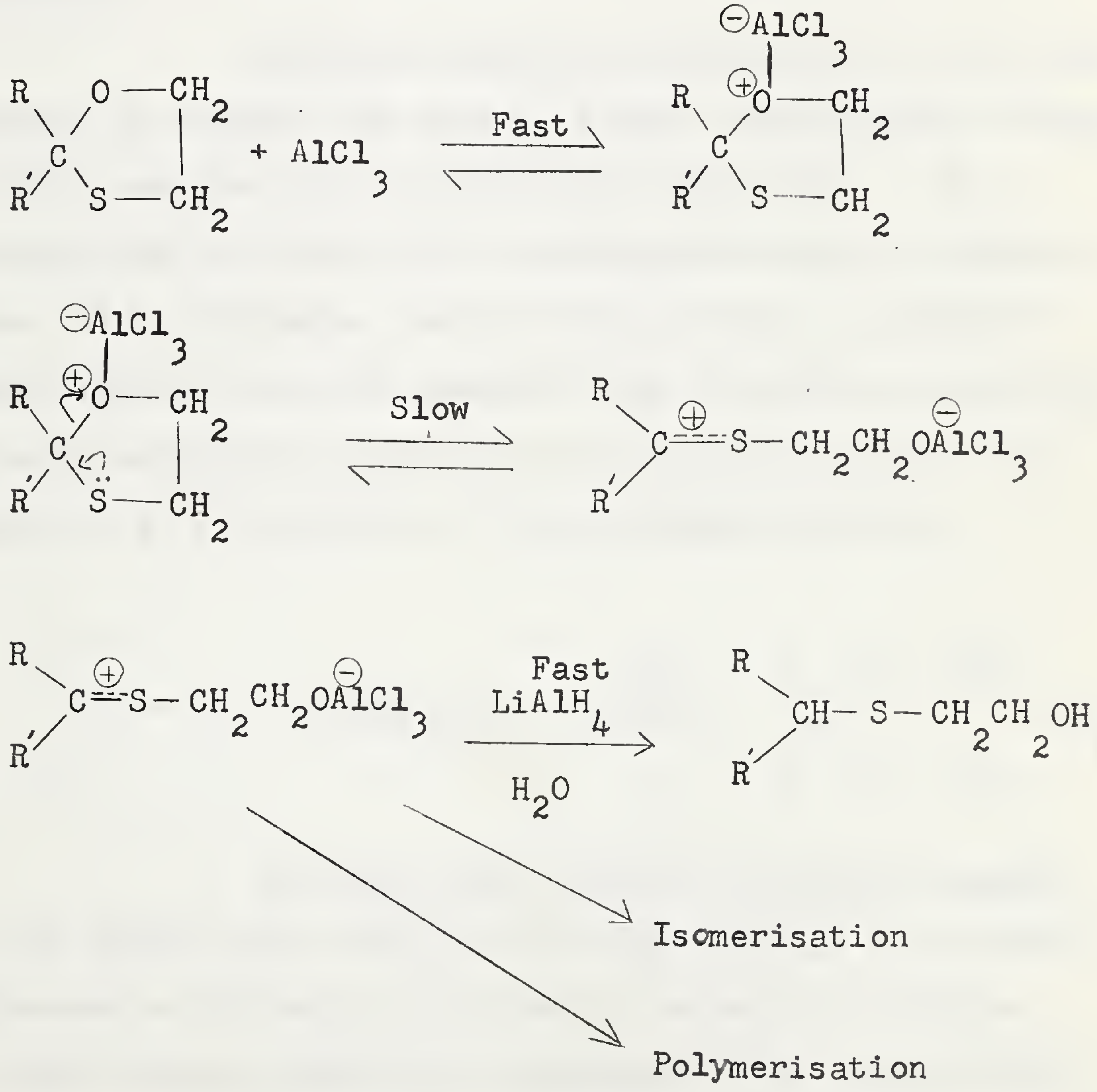
$$BF_3 + 3LiBH_4 \longrightarrow 2B_2H_6 + 3LiF$$

Complete failure of reduction in our case (Expt. 4, Table III) wherein the ratio of boron trifluoride to hydride was only 1:1 could thus be attributed to the total conversion of the Lewis acid, boron trifluoride, to aluminum fluoride. Since the insolubility of aluminum fluoride makes it an ineffective Lewis acid (43) no reduction of the oxathiolane would occur even though the reducing species, lithium borohydride, was present.

In the reduction of oxathiolanes by lithium aluminum hydride and boron trifluoride, a competitive reaction must take place between the acetal and the hydride for the Lewis acid. Co-ordination of the Lewis acid with the oxathiolane would result in subsequent hydrogenolysis, while reaction with the hydride would lead to the formation of an aluminum fluoride and diborane.Such a competitive reaction explains very nicely the variability in amounts of reduction obtained by the use of different orders of addition of reagents. Also the fact that Abdun-Nur and Issidorides (20), Eliel et al.(21) and ourselves (cf. Part II of this

discussion) were able to reduce dioxolanes and dioxanes in excellent yield by the use of this combination can readily be explained by the more facile reduction of these compounds. Hence in the competition for the Lewis acid, the dioxolanes and dioxanes will be favoured over the lithium aluminum hydride and consequently reductive cleavage will occur.

A mechanistic scheme that will fully explain the experimental observations that have been presented and discussed in the preceeding pages is presented below.

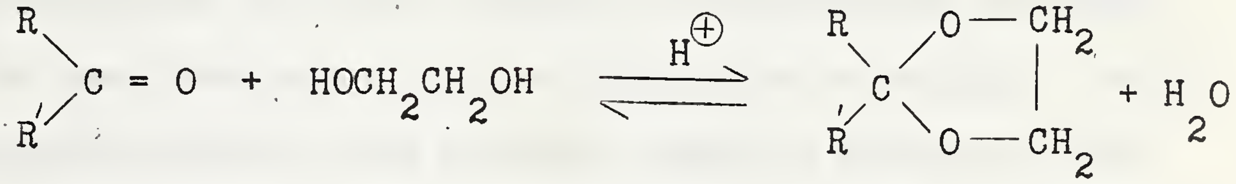

+ AlCl3
Fast
Slow
Fast
LiAlH4
H2O
Isomerisation
Polymerisation

PART II The Reductive Cleavage of Cyclic Acetals and Ketals by Lithium Aluminum Hydride in the Presence of Lewis Acids.

Preparation of Cyclic Acetals and Ketals

Before proceeding with the discussion of the results obtained from the study of the reductive cleavage of acetals and ketals, mention will be made, at this point, of the various methods employed to prepare these compounds.

Numerous methods are available for the preparation of acetals and ketals, a most comprehensive review of which has been made by Wagner and Zook (44). The methods used to prepare the starting materials, 1,3-dioxolanes and 1,3-dioxanes, used in this study, were mainly adaptations of the most commonly used procedures involving the acid-catalysed condensation of alcohols and carbonyl compounds as illustrated by the following equation.

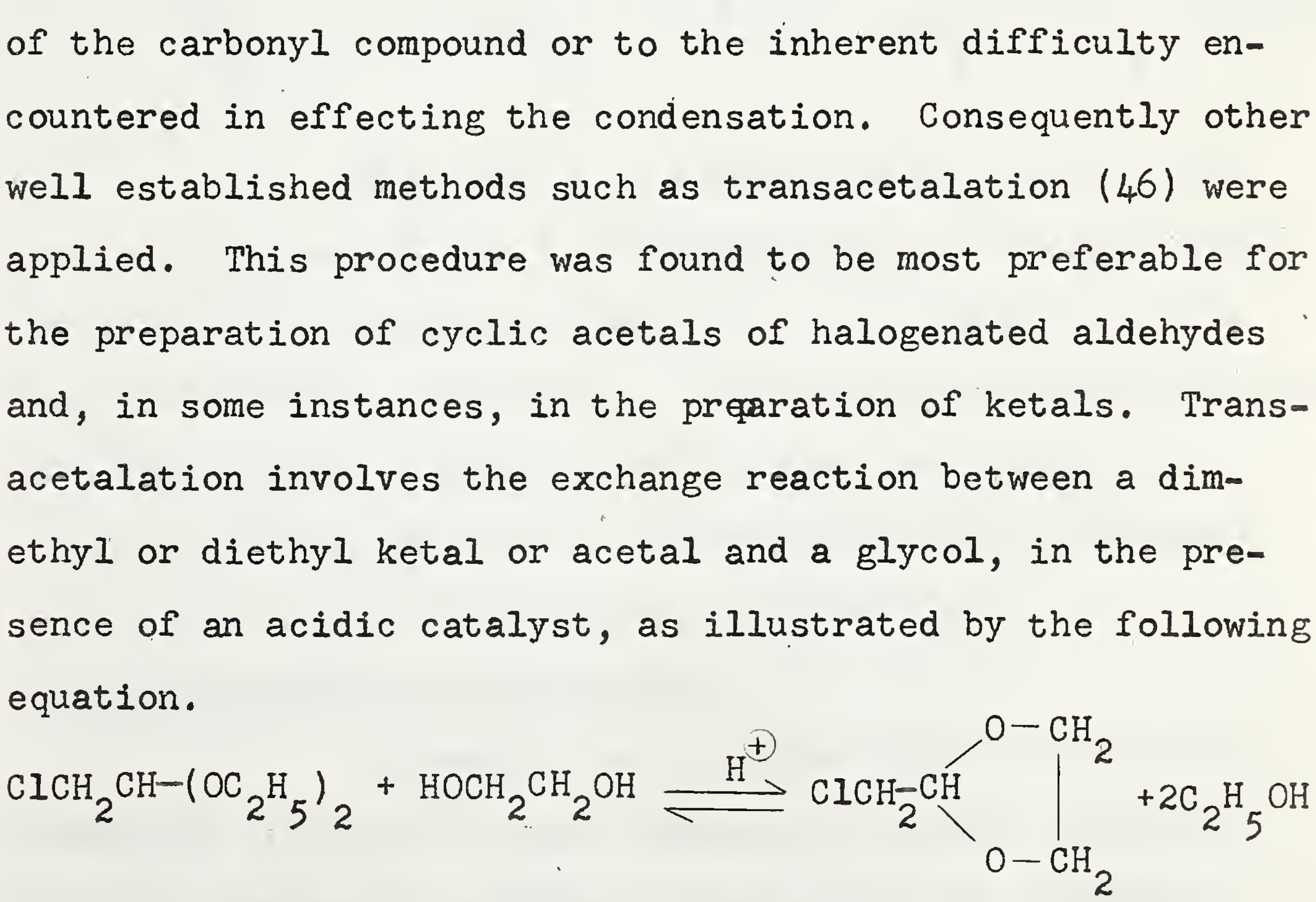


In cases where both the carbonyl compound and the glycol were sufficiently high-boiling, the condensation was effected by refluxing in benzene or toluene. The water formed during the condensation was removed from the reaction site by means of azeotropic distillation with

the solvent using a Dean and Stark water-separator (32) as advocated by Djerassi and Gorman (31).

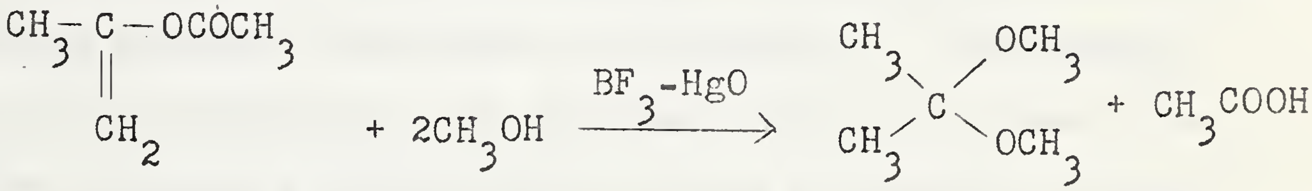
In instances where the carbonyl compound was too low-boiling for the water-separator technique to be employed efficiently, the condensation was effected by allowing the reaction to proceed at room temperature, in the presence of a dehydrating agent and in an inert solvent such as benzene. However when ketones were being condensed by this method, an excess of the ketone served as the solvent (45).

The direct interaction of the carbonyl compound with the requisite glycol proved inadequate, in a few instances, to prepare the necessary 1,3-dioxolane or 1,3-dioxane. This was due either to the non-availability of the carbonyl compound or to the inherent difficulty encountered in effecting the condensation. Consequently other well established methods such as transacetalation (46) were applied. This procedure was found to be most preferable for the preparation of cyclic acetals of halogenated aldehydes and, in some instances, in the preparation of ketals. Transacetalation involves the exchange reaction between a dimethyl or diethyl ketal or acetal and a glycol, in the presence of an acidic catalyst, as illustrated by the following equation.



The equilibrium set up during the reaction is shifted completely to the right by removal of the liberated alcohol by distillation during the reaction.

Finally another method that should be mentioned here although it is not of general applicability is that of reaction of alcohols with vinyl esters (47). This method was used in one instance only during this investigation and that was for the preparation of a precursor of a required ketal. This method entails the reaction between aliphatic alcohols and either vinyl or isopropenyl esters in the presence of a boron trifluoride-mercuric oxide catalyst as shown by the following equation.



The choice of substituents at the 2- and the 4- positions of the 1,3-dioxolane and 1,3-dioxane rings was governed to a large extent by the availability of the requisite starting materials. Even so a satisfactory spectrum of substituents, ranging from electron donors, such as phenyl and alkyl groups, to strongly electron withdrawing groups such as trichloromethyl, was obtained.

General Methods of Hydrogenolysis

Although the procedure used to effect the reductive cleavage of these compounds is amply described in the experimental section, a review of this procedure

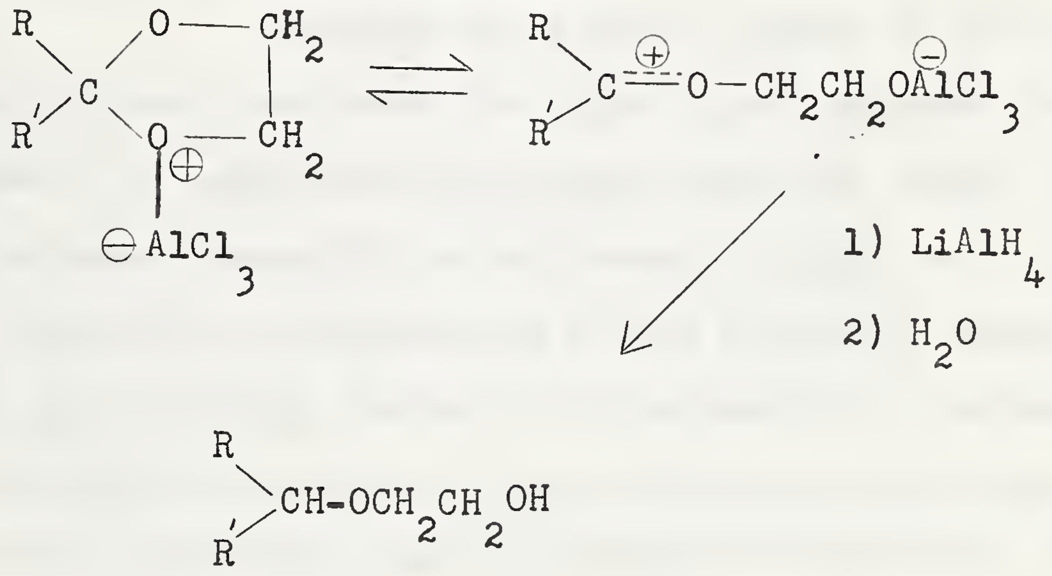
here seems well justified.

The most satisfactory procedure for the hydrogenolysis of acetals and ketals was found to be identical to that used to effect the reductive cleavage of the hemithioacetals and ketals which has been described fully in the preceding section. This procedure entails the addition of an etheral solution of the Lewis acid to a solution of the acetal or ketal in ether to which the requisite amount of lithium aluminum hydride had been added. As was found in the case of the sulphur acetals, if the order of addition of the reagents was reversed, and the Lewis acid and acetal or ketal mixed, in ether solution, prior to the addition of the lithium aluminum hydride, then a considerable amount of resinous material was found in the product. Consequently all of the reductions were performed using the former procedure, including those in which boron trifluoride was employed as the Lewis acid.

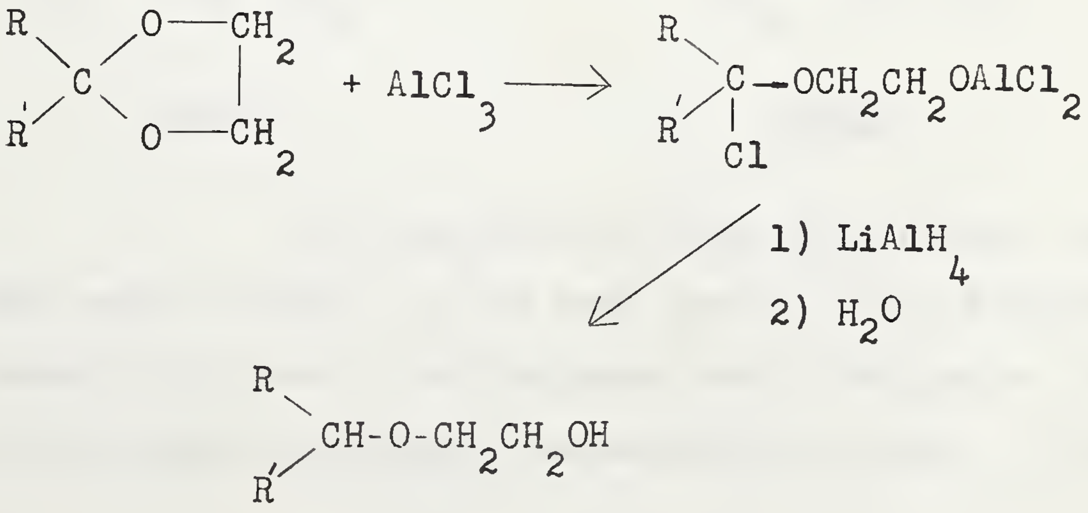
In the preceding section dealing with the hydrogenolysis of the sulphur acetals and ketals it was noted that when boron trifluoride was used to promote the reduction, the order of addition of the reagents was such that the Lewis acid and the hemithioacetal or ketal were mixed prior to the addition of the lithium aluminum hydride in order to obtain optimum amounts of reduction. This procedure was not necessary to effect the reduction of the fully oxygenated acetals and ketals due to the greater ease with which the compounds are reduced (cf. Page 27)

DISCUSSION OF RESULTS

Two possible mechanisms for thehydrogenolysis of acetals and ketals, by lithium aluminum hydride in the presence of Lewis acids, have previously been suggested (18). One involves hydride attack on the complex formed from the Lewis acid and the acetal or ketal, as illustrated by the following equation.


R
R'
C
O
CH2
CH2
O
AlCl3
R
R'
C
O-CH2CH2OAlCl3
1) LiAlH4
2) H2O
R
R'
CH-OCH2CH2OH

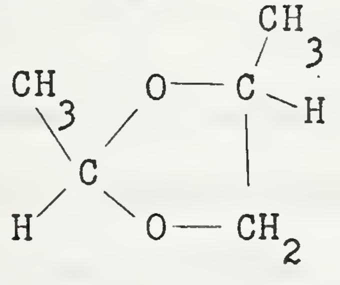
The second suggested mechanism requires the prior formation of an ∝-haloether which may then be readily reduced as illustrated below.


R
R'
C
O
CH2
CH2
O
+ AlCl3
R
R'
C
OCH2CH2OAlCl2
Cl
1) LiAlH4
2) H2O
R
R'
CH-O-CH2CH2OH

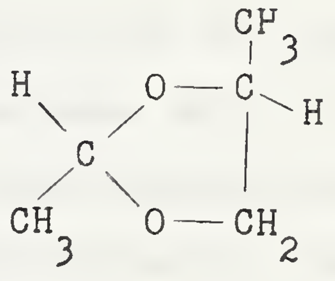
Up to now, no conclusive evidence has been forwarded in the literature in support of either of these two mechanistic schemes.

This discussion will be directed in such a manner as to attempt to obtain a formal analogy between the mechanistic route of hydrogenolysis of acetals and ketals with that of the well established mechanism of the hydrolysis of these compounds.

During the initial stages of this study, the discovery was made that with 1,3-dioxolanes that were capable of exhibiting cis-trans isomerism, namely those dioxolanes containing substituents at both the 2- and the 4- positions as illustrated by the following example of the cis and trans isomers of 2,4-dimethyl-1,3-dioxolane, the relative amounts of C_2-O_1 and C_2-O_3 bond cleavage was entirely dependent upon the relative proportions of the isomers present.



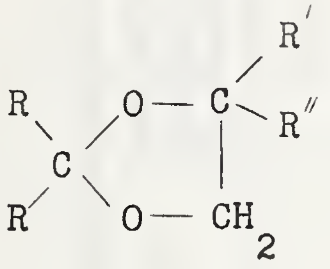
cis

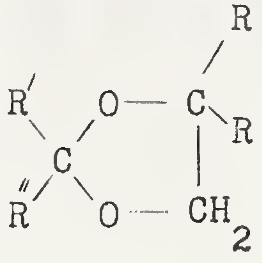


trans

In the light of this observation, the study was confined, in the most part, to the reductive cleavage of those 1,3-dioxolanes and 1,3-dioxanes that do not exhibit cis-trans isomerisation, namely, those

compounds possessing two identical substituents at either the 2- or 4- positions of the ring as illustrated by the following structures and to those substituted in either the C_2 or C_4 position.





However in two cases it has been found possible to achieve separation of the *cis* and *trans* isomers of a particular 1,3-dioxolane in quantities large enough to undertake a study of their hydrogenolysis. The results of this particular aspect of the investigation will also be discussed.

A. Effect of Substituents at the 2-Position upon the Ease of Reduction of 1,3-Dioxolanes.

The results obtained from the reduction of a number of 2-substituted-1,3-dioxolanes with a combination of lithium aluminum hydride and aluminum chloride are given in Table V, Page 59. The extent of reduction in a given time can be considered as a rough measure of the rate of ring cleavage and reduction, since the reduction step is irreversible. Accuracy depends upon the recovery of the total reaction products which include both reduction product and, where reduction is not complete, the unchanged starting material. The yields obtained in

TABLE V

Reduction of 2-Substituted-1,3-dioxolanes with a Combination of Lithium Aluminum Hydride and Aluminum Chloride

Expt.	Dioxolane	Reduction Product	Total Recovery %[a]	Reduction Product in Recovered Product %	Time
1.	2-Phenyl-1,3-dioxolane	2-Benzyloxyethanol	80	100	60 min
2.	2,2-Dimethyl-1,3-dioxolane	2-*iso*Propoxyethanol	70	100	60 min
3.	2-Methyl-1,3-dioxolane	2-Ethoxyethanol	70	100	60 min
4.	1,3-Dioxolane	2-Methoxyethanol	55	60	24 hr.
5.	2-Chloromethyl-1,3-dioxolane	2-β-Chloroethoxyethanol	80	14	48 hr.
6.	2-Dichloromethyl-1,3-dioxolane	——	85	0	48 hr.
7.	2-Trichloromethyl-1,3-dioxolane	——	76[b]	0[b]	48 hr.
8[c]	2-Trichloromethyl-1,3-dioxolane	——	82[b]	0[b]	2 hr.

[a] Total Recovery includes unchanged starting material and reduction product.

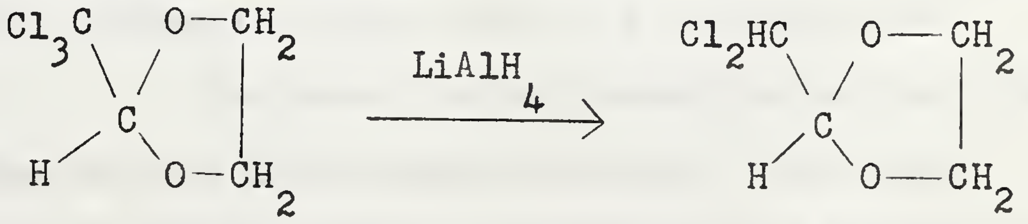
[b] The recovered material was 2-dichloromethyl-1,3-dioxolane, no material resulting from the reductive cleavage of the dioxolane ring was detected.

[c] The reduction was carried out with lithium aluminum hydride alone.

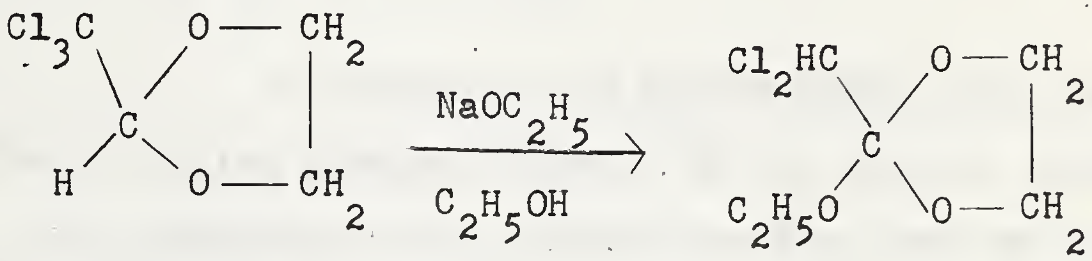
these reductions are generally sufficiently good to show at least qualitatively the relative rate of reduction.

If the ease of reduction of 1,3-dioxolane is taken to be the norm, this compound was found to be less than half reduced in 24 hours whereas 2-methyl-, 2,2-dimethyl- and 2-phenyl-1,3-dioxolane are fully reduced in 60 minutes and it is quite likely that these compounds are fully reduced in much less than this allotted time. On the other hand 2-chloromethyl-1,3-dioxolane is reduced only to the extent of 14% even after 48 hours and more strongly electron withdrawing substituents such as the *dichloromethyl* group inhibit reduction completely.

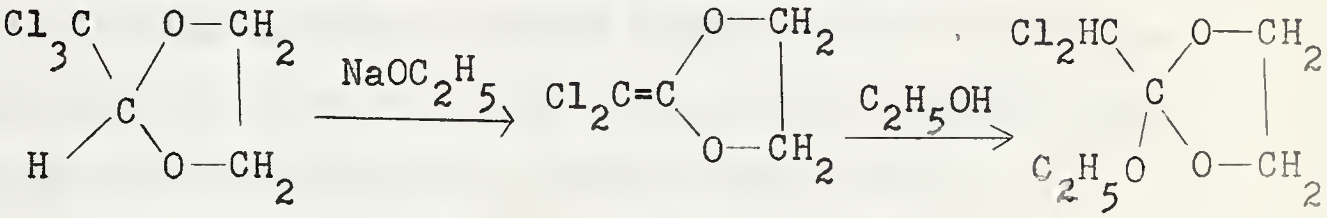
Of some interest is the result of the attempted hydrogenolysis of *2-trichloromethyl-1,3-dioxolane*. The material recovered from this experiment, rather than being either the expected reduction product, 2-β,β,β-trichloroethoxyethanol or the starting material, proved to be *2-dichloromethyl-1,3-dioxolane*. Further work showed that formation of the dichlorocompound from the trichloro precursor could be achieved by the use of lithium aluminum hydride alone although it is conceivable that aluminum chloride could in this case be formed *in situ* during the course of the reaction.



A somewhat analogous result has recently been found by Ruske and Hartmann (48) who studied the action of strong bases, such as sodium ethoxide, upon the same dioxolane. These workers found that 2-trichloromethyl-1,3-dioxolane upon treatment with an ethanolic solution of sodium ethoxide, afforded 2-dichloromethyl-2-ethoxy-1,3-dioxolane as indicated by the following equation.


Cl_3C
O — CH_2
C
H
O — CH_2
$NaOC_2H_5$
C_2H_5OH
Cl_2HC
O — CH_2
C
C_2H_5O
O — CH_2

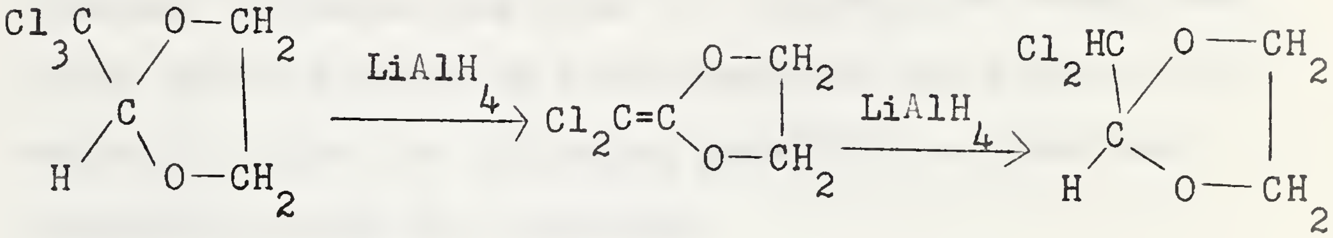
The workers postulated the prior elimination of hydrogen chloride from the trichloromethyl compound, followed by the addition of ethanol to the intermediate 2-dichloromethylene-1,3-dioxolane as illustrated by the following equation.


Cl_3C
O—CH_2
C
H
O—CH_2
$NaOC_2H_5$
Cl_2C=C
O—CH_2
O—CH_2
C_2H_5OH
Cl_2HC
O—CH_2
C
C_2H_5O
O—CH_2

The elimination of the hydrogen chloride was brought about by the attack of the base on the strongly acidic C_2 hydrogen atom, followed by departure of a chloride ion.

The same line of reasoning may very well hold true for the case under discussion. The basic character of lithium aluminum hydride could promote the

elimination of hydrogen chloride from the 2-trichloromethyl-1,3-dioxolane, the resulting 2-dichloromethylidene-1,3-dioxolane, then being reduced by the hydride, to give the observed product, by the following scheme.



The reduction of double bonds upon treatment with lithium aluminum hydride is not without precedent. For instance, allyl alcohol has been reduced to 1-propanol (49), ω-nitrostyrene to β-phenylethylamine (50) and α-ethylcrotonamide to β-ethylbutylamine (51) to mention a few cases.

The possibility of direct replacement of a chlorine atom of the trichloromethyl group by a hydrogen atom via an SN_2 substitution seems to be rather doubtful as lithium aluminum hydride reduction of chloral hydrate has been found to yield β,β,β-trichlorethanol, thus leaving the trichloromethyl moiety intact (52).

No information as to the relative ease of reduction of the first three dioxolanes in Table V could be gleaned from an inspection of the amount of reduction occurring in the allotted reaction time. All of these compounds were completely reduced in 1 hour and it is more than likely that the time required for total reduction is considerably less than this as we have previously

seen that an analogous dioxolane, 2-n-propyl-1,3-dioxolane, is completely reduced within 20 minutes (cf. page 27).

A purely qualitative estimation as to the relative ease of reduction of these dioxolanes was obtained by subjecting them to a competitive reduction. If we take a mixture of two dioxolanes and subject it to reduction, then the following parallel reactions are occurring during the reduction.

$$\text{DIOXOLANE (1)} \xrightarrow[k_1]{AlCl_3 + LiAlH_4} \text{REDUCTION PRODUCT (1)}$$

$$\text{DIOXOLANE (2)} \xrightarrow[k_2]{AlCl_3 + LiAlH_4} \text{REDUCTION PRODUCT (2)}$$

If the extent of reduction is limited so that the concentrations of each of the dioxolanes remained essentially constant throughout the reduction, and also assuming that the dioxolane molecule participates in the rate determining step or steps then the relative ratio of reduction of the two dioxolanes will be proportional to the relative amounts of reduction product formed from the reduction of each of the dioxolanes.

$$k_2 : k_1 = \left[\text{Reduction Product (2)}\right] : \left[\text{Reduction Product (1)}\right]$$

Accordingly equimolar binary mixtures of 2-methyl-, 2,2-dimethyl-, and 2-phenyl-1,3-dioxolane were subjected to competitive reductions with the amount of reduction being allowed to proceed only to the extent of

approximately 10% to 15% by the use of limited quantities of reducing agent. The results of these experiments are to be found in Table VI (Page 65).

From a study of these results and also taking into account the results given in Table V the following series of groups can be arranged in order of their decreasing ability to enhance the reductive cleavage of 1,3-dioxolanes when present at the C_2 position of the dioxolane ring.

$$C_6H_5 - > (CH_3)_2 - > CH_3 - \gg H_2 - > ClCH_2 - > Cl_2CH -$$

This order is in direct accord with the stability of the corresponding substituted carbonium ions.

B. Effect of Substituents at the C_4 Position of the 1,3-Dioxolane Ring upon the Rate of Reduction.

The effect of substituents at the C_4 position of the 1,3-dioxolane ring is nowhere near as pronounced as that of the same substituents at the C_2 position. This effect has been more clearly demonstrated in the reduction of formals rather than with the corresponding 2,2-dimethyl-4-substituted-1,3-dioxolanes as the two methyl substituents at the C_2 position were found to accelerate the rate of reduction to such a degree that in all cases complete reduction occurred in the allotted time and hence no comparison of the ease of reduction could readily be obtained. However when the formals were used in the investigation a clear gradation in the

TABLE VI

A Study of the Competitive Reduction of 2-Substituted-1,3-Dioxolanes with Lithium Aluminum Hydride and Aluminum Chloride *

Expt.	Dioxolanes	Total Recovery %	Relative Amounts of Reduction Products (Mole %)		Ka/Kb
1.	a 2-Phenyl-1,3-dioxolane	81	2-Benzyloxyethanol	89	8
	b 2,2-Dimethyl-1,3-dioxolane		2-*iso*Propoxyethanol	11	
2.	a 2-Phenyl-1,3-dioxolane		2-Benzyloxyethanol	*ca*.100%	
	b 2-Methyl-1,3-dioxolane	84	2-Ethoxyethanol	negligible	≫1
3.	a 2,2-Dimethyl-1,3-dioxolane		2-*iso*Propoxyethanol		
	b 2-Methyl-1,3-dioxolane	77	2-Ethoxyethanol	**	>1

* Reaction time in each experiment was 30 minutes, the extent of reduction was controlled so that approximately 15% of the total dioxolane was hydrogenolysed.

** Analysis of Reduction products performed by N.M.R. which indicated a large majority of 2-*iso*propoxyethanol. No separation of the reduction products could be obtained by v.p.c. analysis.

TABLE VII

The Reduction of 4-Substituted-1,3-Dioxolanes with Lithium Aluminum Hydride and Aluminum Chloride I

Dioxolane	Reduction Time (hr.)	Total Recovery,[a] %	Recovered[b] starting material,%	Reduction[b] Product,%
4-Methyl-1,3-dioxolane	1.5	85	8	92
4,4-Dimethyl-1,3-dioxolane	24	67	16	84
4-Phenyl-1,3-dioxolane	60	83	25	75
1,3-Dioxolane	24	55	40	60
4-*iso*Propoxymethyl-1,3-dioxolane	48	93	34	66
4-Chloromethyl-1,3-dioxolane	48	93	70	30

[a] Total recovery includes both reduction product and recovered starting material.

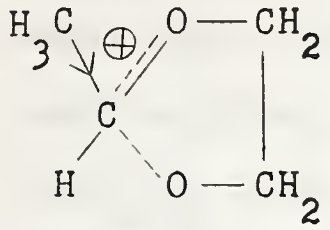
[b] Figures represent percentages of total recovery.

ease of reduction could be detected. The results obtained in this study are to be found in Table VII Page 66.

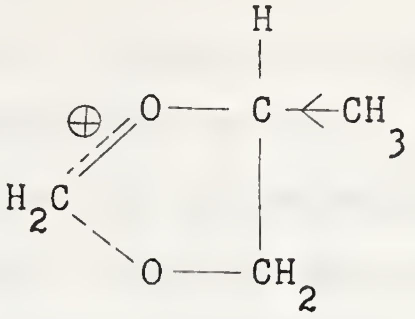
The presence of electron-donating groups at the C_4 position is seen to enhance the rate of reduction although to a much less extent than the same substituent does when at the C_2 position. For instance, 4-methyl-1,3-dioxolane is reduced to the extent of 92% in 90 minutes whereas 1,3-dioxolane is only 60% reduced even after 24 hours. On the other hand electron withdrawing substituents at the C_4 position are again found to have an adverse effect upon the rate of reduction. For instance 4-chloromethyl-1,3-dioxolane is reduced to the extent of 30% in 48 hours whereas 2-chloromethyl-1,3-dioxolane is only 14% hydrogenolysed in the same time.

It is interesting to note the phenyl substituent at the C_4 position plays little or no part in increasing the rate of reduction of 1,3-dioxolanes.

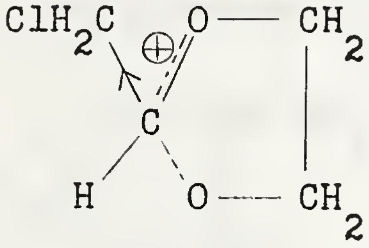
In section A the results showed a correlation between the ease of reduction of 2-substituted -1,3-dioxolanes and the stability of the carbonium ion found at the C_2 position. It is therefore likely that groups at the C_4 position will have far less effect upon the stability of an incipient carbonium ion at the C_2 position itself, as indicated in the following structures.



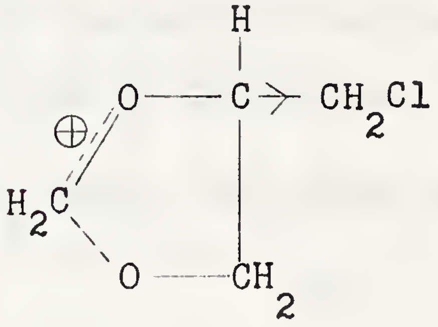
Greater stability of incipient oxocarbonium ion



Less stability of incipient oxocarbonium ion



Destabilisation of incipient oxocarbonium ion



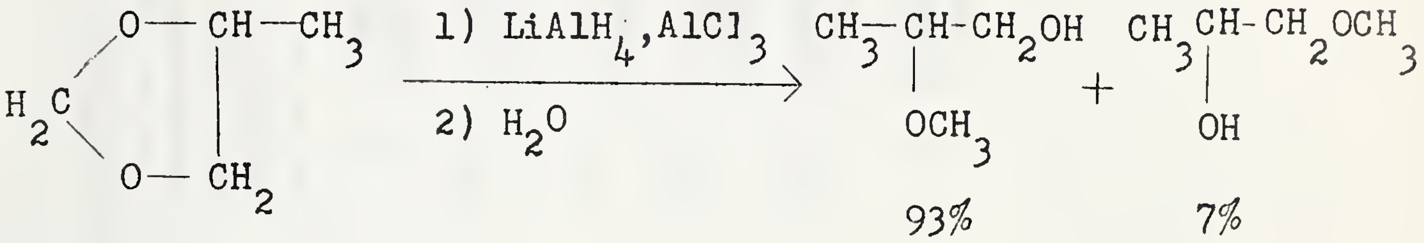
Destabilisation of incipient oxocarbonium ion but to a lesser degree

The results found so far can be rationalised by the concept that formation of the oxocarbonium ion is involved in the rate determing step of the hydrogenolysis. Further evidence will be offered to support this concept in the following material.

C. Effect of Substituents at the C_4 Position upon the Direction of Ring opening during the Reductive Cleavage of 1,3-Dioxolanes.

Substituents at the C_4 position of the dioxolane ring have a profound effect upon the direction of ring opening when the dioxolane is subjected to reduction with lithium aluminum hydride in combination with Lewis acids. Table VIII serves to illustrate the results obtained during a study of the hydrogenolysis of

4-substituted-1,3-dioxolanes. A survey of these results shows that electron-donating groups at the C_4 position tend to direct the cleavage of the 1,3-dioxolane ring at the C_2-O_1 bond preferentially. This is ably demonstrated in the reductions of 4-methyl-1,3-dioxolane and 2,2,4-trimethyl-1,3-dioxolane where 93% and 82%, respectively, of the products of reduction is the primary alcohol resulting from cleavage of the C_2-O_1 bond as illustrated.


1) $LiAlH_4$, $AlCl_3$
2) H_2O
CH_3-CH-CH_2OH / OCH_3
+
CH_3CH-CH_2OCH_3 / OH
93%
7%

The reverse is found to be true when electron withdrawing substituents are placed at the C_4 position. In these cases it is found that cleavage of the C_2-O_3 bond is preferred. For instance, hydrogenolysis of 4-chloromethyl-2,2-dimethyl-1,3-dioxolane is found to afford 95% of the product of reduction as the secondary alcohol, produced by cleavage of the C_2-O_3 bond, as illustrated by the following equation.

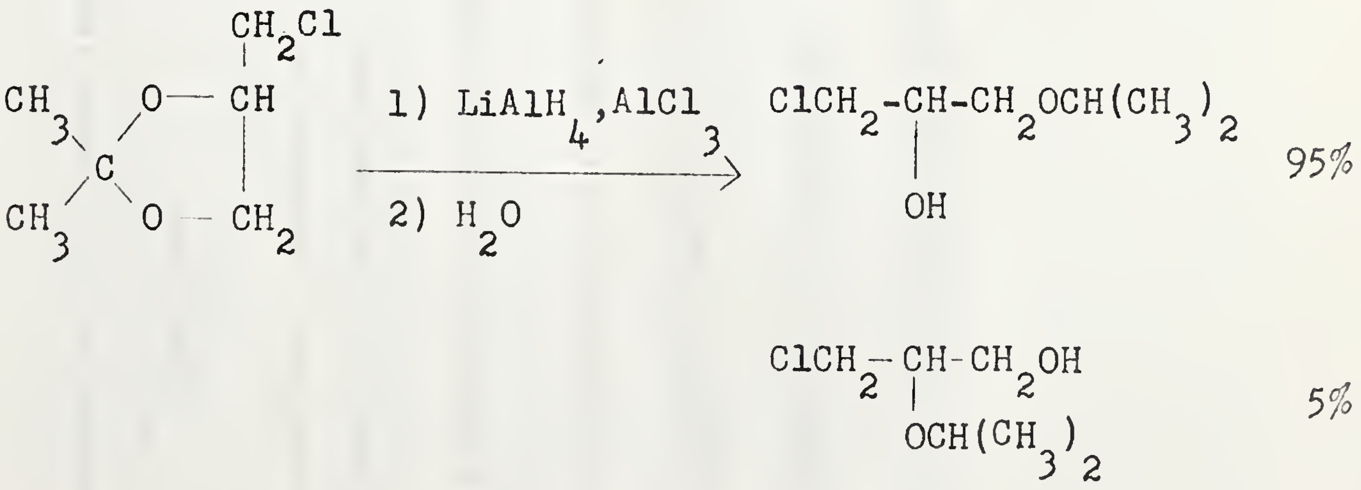

1) $LiAlH_4$, $AlCl_3$
2) H_2O
$ClCH_2$-CH-$CH_2OCH(CH_3)_2$ / OH
95%
$ClCH_2$-CH-CH_2OH / $OCH(CH_3)_2$
5%

TABLE VIII

The Reduction of 4-Substituted-1,3-Dioxolanes with Lithium Aluminum Hydride and Aluminum Chloride.II

Expt.	Dioxolane	Reduction Time	Total Yield,%[a]	Recovered starting material,%[b]	Reduction Products[c]	
1	4-Methyl-1,3-dioxolane	90 min.	85	8	2-Methoxy-1-propanol 1-Methoxy-2-propanol	93% 7%
2	4,4-Dimethyl-1,3-dioxolane	90 min.	49	69	2-Methoxy-2-methyl-1-propanol 1-Methoxy-2-methyl-2-propanol	92% 8%
3	4-Chloromethyl-1,3-dioxolane	48 hr.	93	65	3-Chloro-2-methoxy-1-propanol [d] 1-Chloro-3-methoxy-2-propanol	10% 90%
4	4-*iso*Propoxymethyl-1,3-dioxolane	48 hr.	93	34	3-*iso*Propoxy-2-methoxy-1-propanol[d] 1-*iso*Propoxy-3-methoxy-2-propanol	24% 76%
5	4-Phenyl-1,3-dioxolane	60 hr.	83	25	2-Methoxy-2-phenylethanol 2-Methoxy-1-phenylethanol	73% 27%
6	2,4,4-Trimethyl-1,3-dioxolane	90 min.	85	0	2-Ethoxy-2-methyl-1-propanol 1-Ethoxy-2-methyl-2-propanol	90% 10%

Cont'd on Page 71

TABLE VIII (Cont'd)

Expt.	Dioxolane	Reduction Time	Total Yield,%[a]	Recovered starting material,%[b]	Reduction Products[c]	
7	4,4-Dimethyl-2-phenyl-1,3-dioxolane	90 min.	74	0	2-Benzyloxy-2-methyl-1-propanol 1-Benzyloxy-2-methyl-2-propanol	89% 11%
8	2,2,4-Trimethyl-1,3-dioxolane	90 min.	86	0	2-*iso*Propoxy-1-propanol 1-*iso*Propoxy-2-propanol	82% 18%
9	2,2,4,4-Tetramethyl-1,3-dioxolane	90 min.	87	0	2-*iso*Propoxy-2-methyl-1-propanol 1-*iso*Propoxy-2-methyl-2-propanol	6% 94%
10	4-Chloromethyl-2,2-dimethyl-1,3-dioxolane	90 min.	96	0	3-Chloro-2-*iso*propoxy-1-propanol 1-Chloro-3-*iso*propoxy-2-propanol	5% 95%
11	2,2-Dimethyl-4-*iso*propoxymethyl-1,3-dioxolane	90 min.	71	0	2,3-Di*iso*propoxy-1-propanol[d] 1,3-Di*iso*propoxy-2-propanol	14% 86%
12	2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane	90 min.	79	0	2-*iso*Propoxy-1,3-propandiol 1-*iso*Propoxy-2,3-propandiol	19% 81%
13	2,2-Dimethyl-4-phenyl-1,3-dioxolane	90 min.	81	0	2-*iso*Propoxy-2-phenylethanol 2-*iso*Propoxy-1-phenylethanol	52% 48%

---

[a] Total yield includes both reduction product and recovered starting material

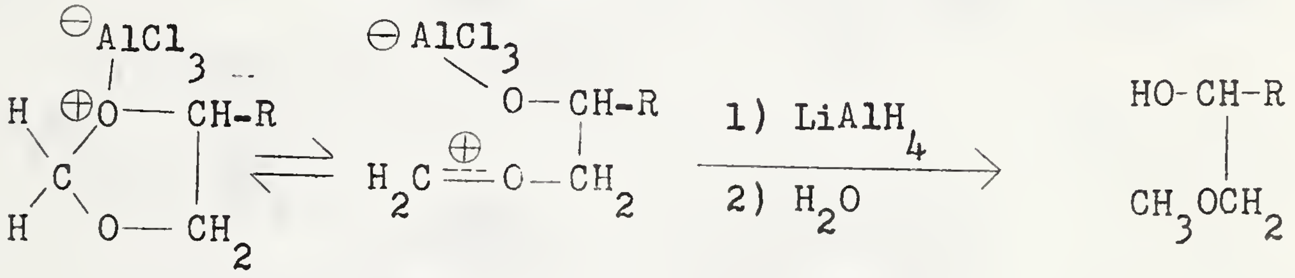
[b] Percent starting material recovered is based upon total yield

[c] Percent of each reduction product based upon total amount of reduction products = 100%

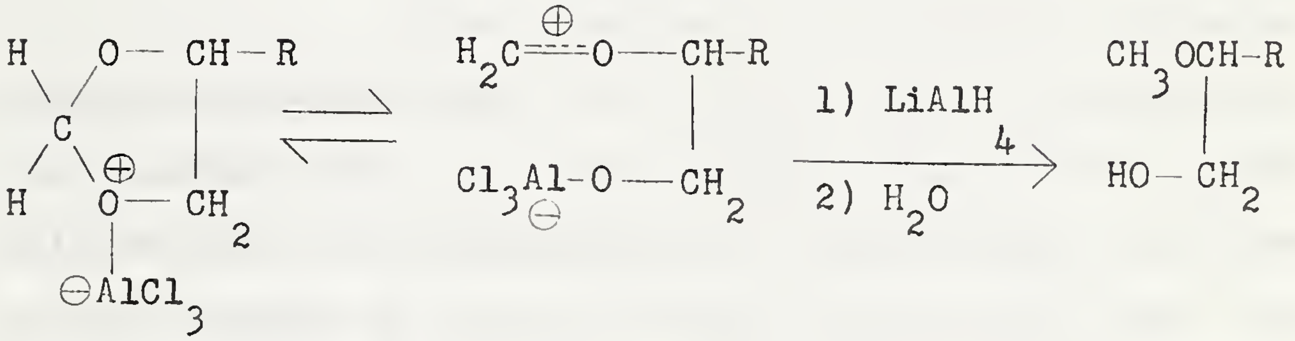
[d] Assumed structure of minor reduction product

These results can quite readily be rationalised by the concept of the formation of a resonance-stabilised oxocarbonium ion as the rate (and hence the product) determining step. The resonance-stabilised oxocarbonium ion may be formed by either cleavage of the C_2-O_1 or C_2-O_3 bonds of the dioxolane ring as illustrated by the following schemes.

Scheme A

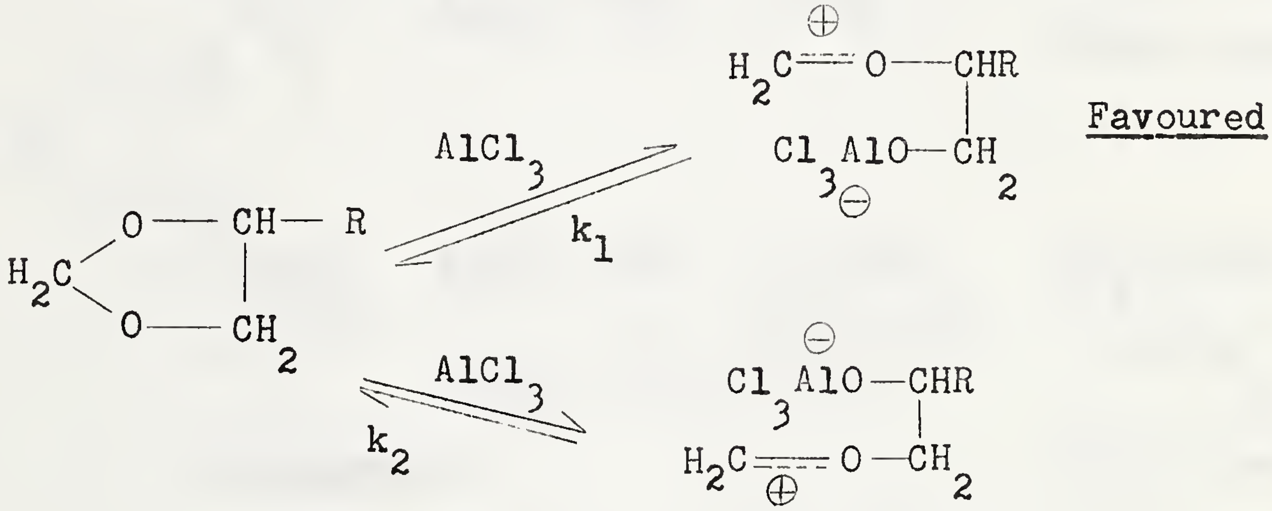


Scheme B



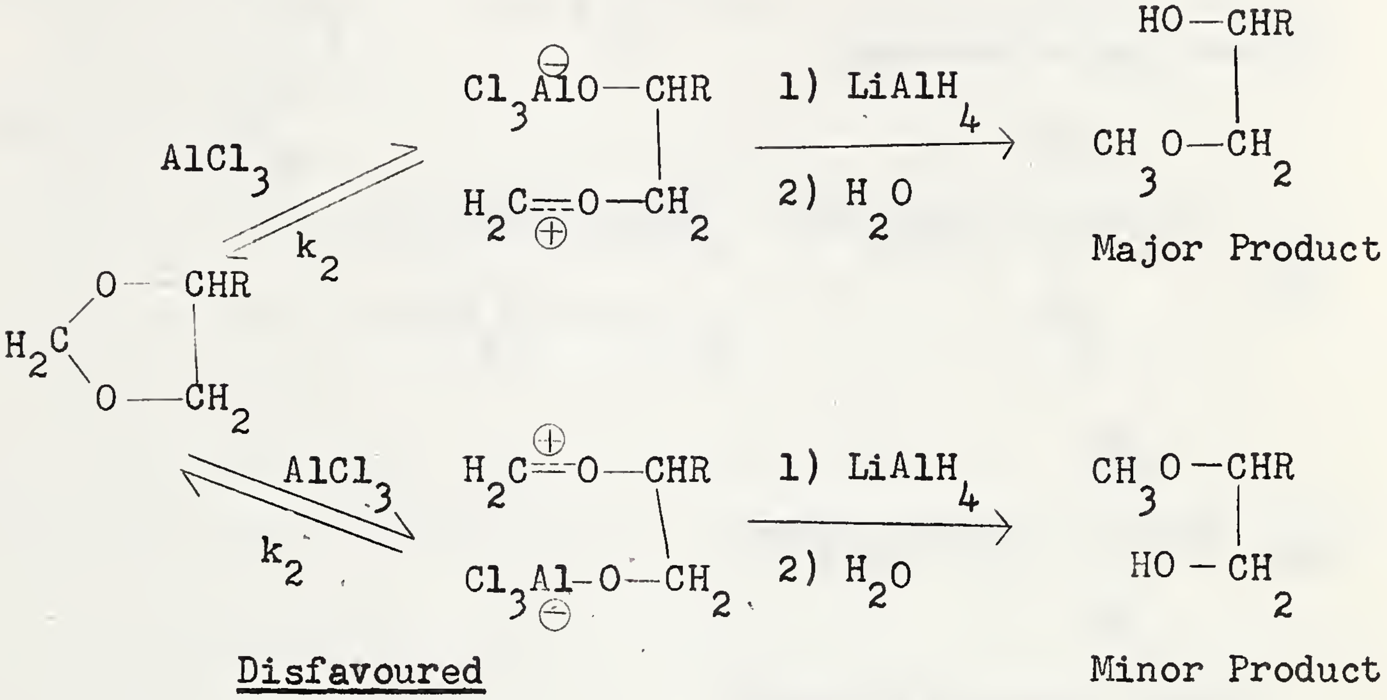
If R represents an electron donating group then this will tend to have the effect of stabilising the oxocarbonium ions in both scheme A and B. However the stabilising effect will be greater in the case of B than in A due to the closer proximity of the electron donating group to the site of the oxocarbonium ion in scheme B. The formation of the more stable oxocarbonium ion will be

preferred over that of the least stable ion and now if we consider the rate-determining step of the reduction to be the formation of the transient oxocarbonium ion then the product arising from the reduction of the preferred ion will be the major constituent of the reduction product as illustrated by the following equation, where R represents an electron donating group.

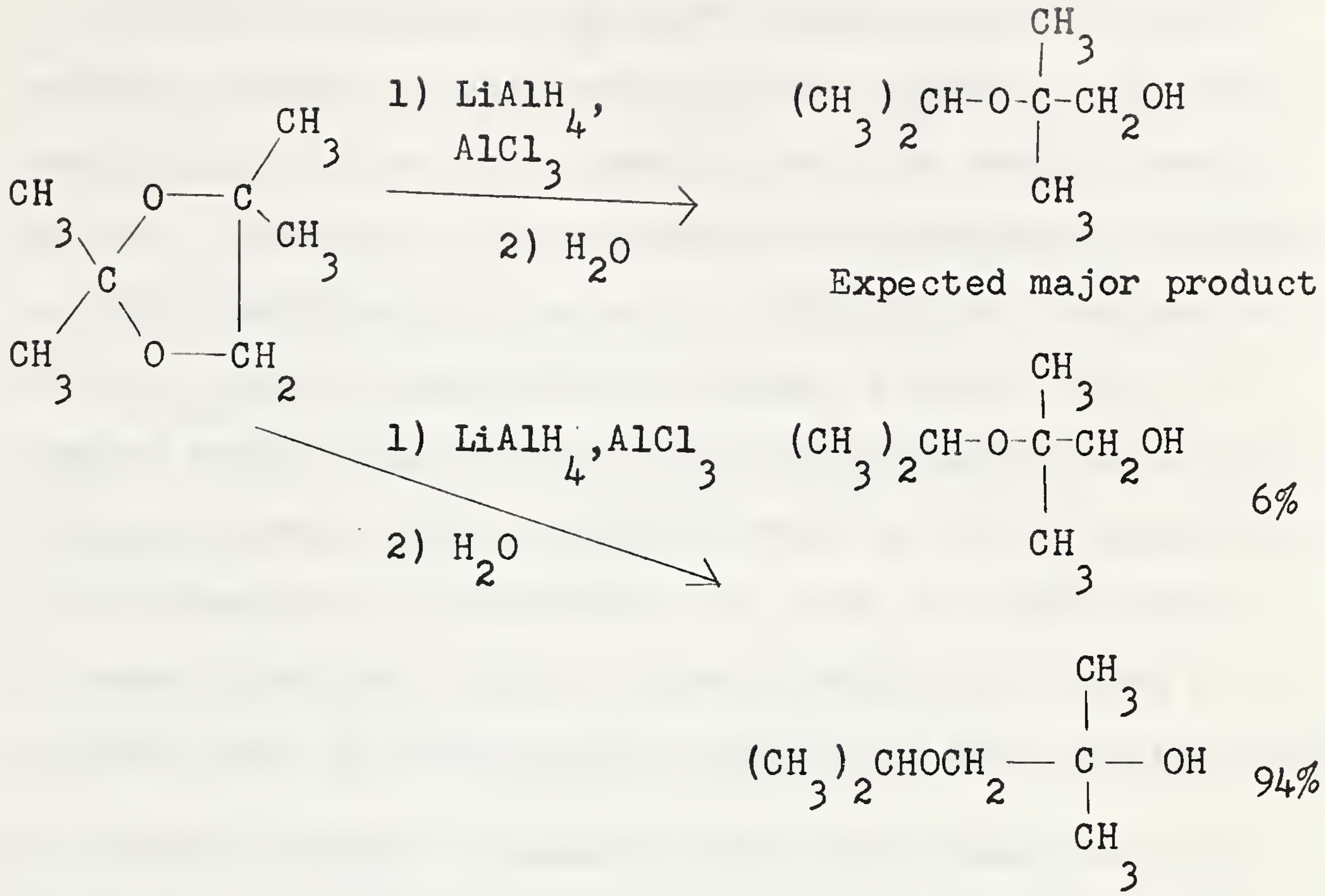


This situation is reversed when electron withdrawing substituents are present at the C_4 position of the dioxolane ring. In this case the effect of the C_4 substituent will be to destabilise the oxocarbonium ions formed by the cleavage of either the C_2-O_1 or the C_2-O_3 bond. This destabilisation of the incipient oxocarbonium ions will tend to disfavour their formation and hence will decrease the overall rate of hydrogenolysis of 1,3-dioxolanes as has been found in the preceding section. However this destabilising effect will be greatest for the oxocarbonium ion closest to the electron withdrawing substituent. Thus the formation of this ion will be repressed to a greater extent

than will be the formation of the other possible ion as illustrated by the following scheme, in which R represents an electron withdrawing group.


AlCl$_3$
k$_2$
$Cl_3\overset{\ominus}{Al}O$—CHR
$H_2C\overset{\oplus}{=}O$—CH_2
1) $LiAlH_4$
2) H_2O
HO—CHR
CH_3O—CH_2
Major Product
H_2C O—CHR O—CH_2
$H_2\overset{\oplus}{C}=O$—CHR
$Cl_3Al^{\ominus}$—O—CH_2
CH_3O—CHR
HO—CH_2
Minor Product
Disfavoured

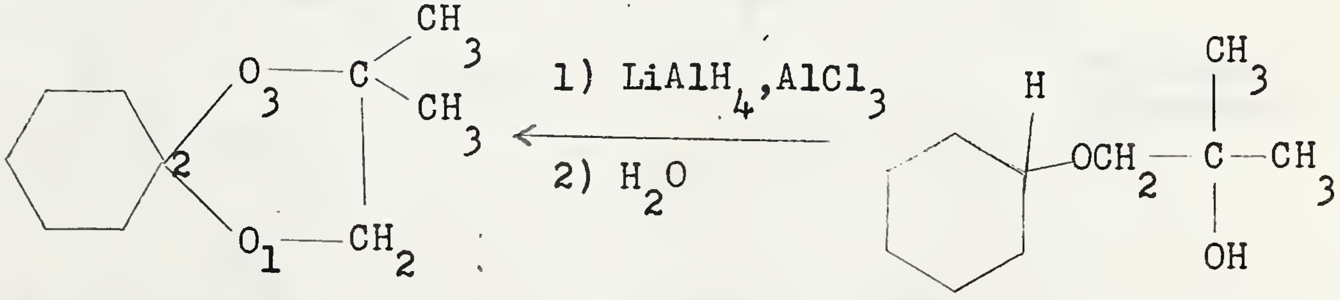
All but one of the results listed in Table VIII agree with this postulation. The single exception, the result obtained from the hydrogenolysis of 2,2,4,4-tetramethyl-1,3-dioxolane (cf. Expt. 9, Table VIII) is at first sight inconsistant with the preceding rationale used to explain the preferential cleavage afforded by C_4 substituents. This particular dioxolane which contains two electron donating substituents at the C_4 position should be expected to afford a preponderance of C_2-O_1 bond cleavage. However, in actual fact, the product obtained is almost exclusively that afforded by C_2-O_3 bond cleavage as indicated by the following equations.


1) LiAlH4, AlCl3
2) H2O
1) LiAlH4, AlCl3
2) H2O
6%
94%

Expected major product

Products actually found

A similar anomoly has also been found by Eliel and co-workers (19) who, upon reduction of cyclohexanone isobutylene ketal, found that only the product afforded by C_2-O_3 bond cleavage was obtained as shown by the following equation.

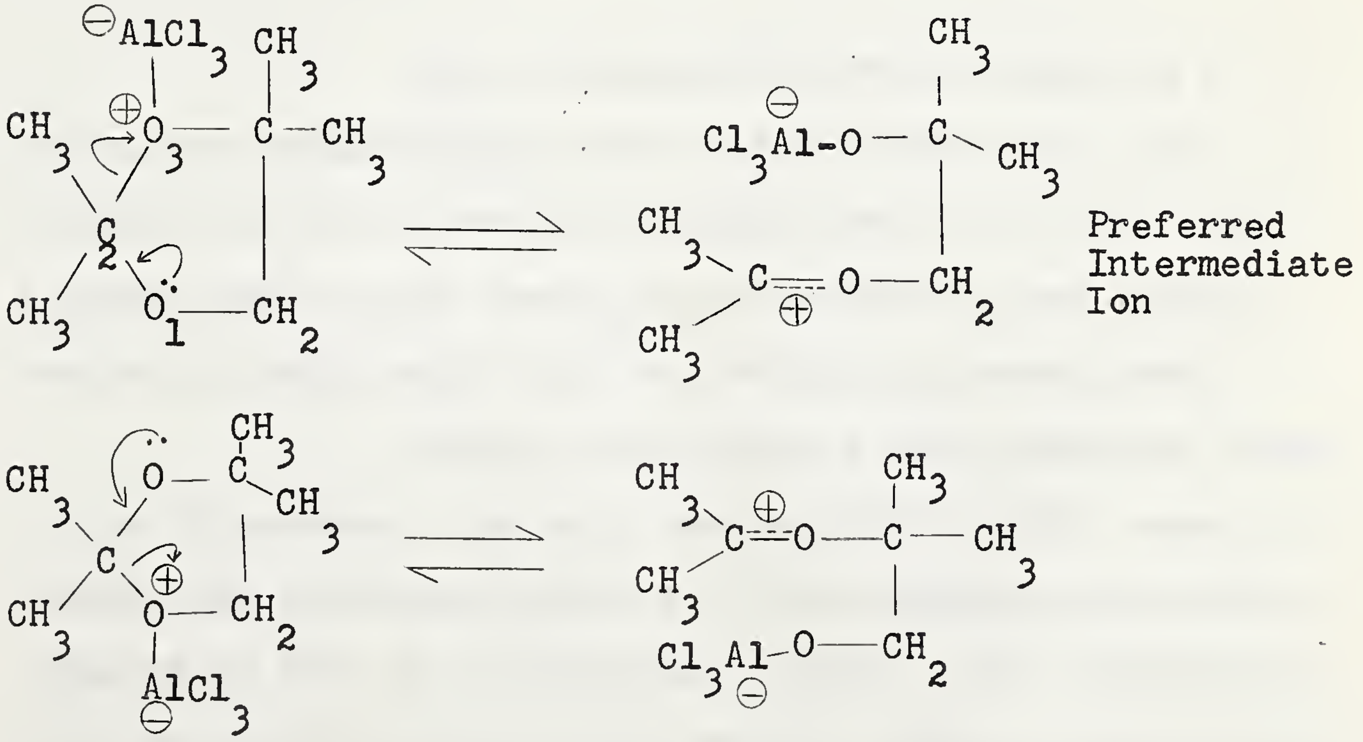

1) LiAlH4, AlCl3
2) H2O

Only product

Two explanations may be offered to account for this unexpected direction of ring cleavage.

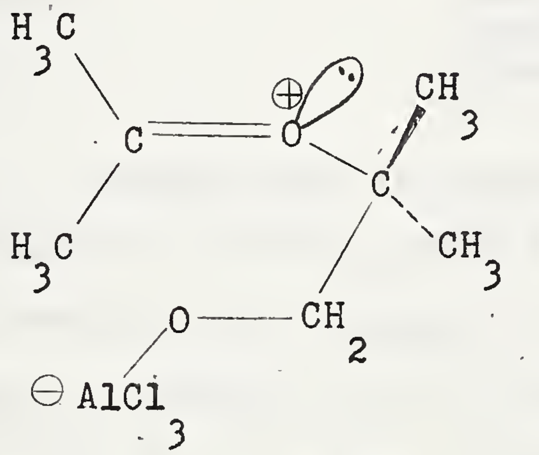
1. The steric strain between the substituents at the C_2 and C_4 positions outweighs the polar influence which should normally control the direction of ring opening. The corresponding 1,3-dioxolane carrying only one methyl group at the C_2 position, 2,4,4-trimethyl-1,3-dioxolane, reduces to give predominantly the product afforded by cleavage of the C_2-O_1 bond as expected (cf. Expt. 8 Table VIII). A similar result was obtained from the corresponding 1,3-dioxolane carrying only one methyl group at the C_4 position, 2,2,4-trimethyl-1,3-dioxolane (cf. Expt. 6, Table VIII). It seems therefore that the fourth substituent plays a decisive role in directing the opening of the dioxolane ring.

2. Another possible explanation for this anomalous ring opening is that oxocarbonium ion formation, necessary for cleavage of the C_2-O_1 bond, is retarded by the steric influence of the C_2 and C_4 substituents.



Preferred Intermediate Ion

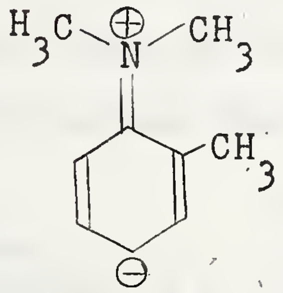
For cleavage of the C_2-O_1 bond to occur, overlap of the p orbitals of the O_3 atom with the developing empty orbital of the C_2 atom must occur with the resulting formation of the oxocarbonium ion. A requirement for obtaining overlap of the p orbitals and hence obtaining double bond formation, is a configuration in which the C_2 atom and its two substituents, the O_3 atom and its lone pair electron orbital and the substituted C_4 atom are all coplanar as indicated below.



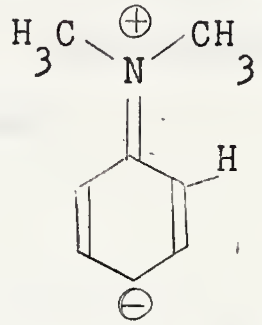
This configuration would result in a strong non-bonded interference between the methyl substituents at the C_2 and the tertiary group on O_3 and thus a strain would occur during the formation of the oxocarbonium ion which would tend to inhibit its development.

Certain anologies to this situation appear in the literature. One such anology (53) is that used to explain the anomalous basicity of N,N-dimethyl-o-toluidine compared to that of N,N-dimethyl aniline. The observation that the o-methyl substituent greatly enhances the basicity

of the amine group is explained by the steric interaction of the o-methyl and N-methyl groups diminishing the contribution of such resonance structures as illustrated by the following structures.



Less sterically
possible
(More basic)

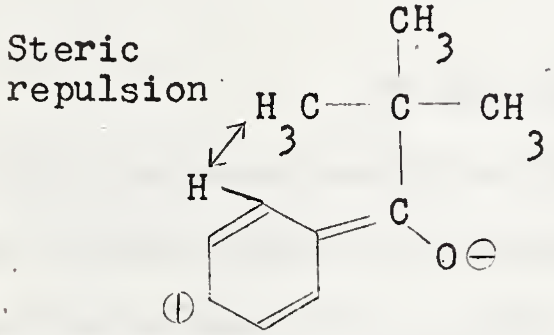


More sterically
possible
(Less basic)

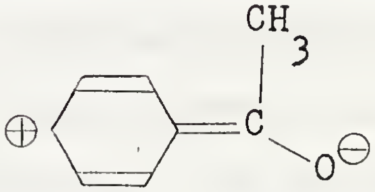
In the case of o-methyl-N,N-dimethylaniline the steric interaction of the o-methyl and N-methyl groups prevents the formation of a coplanar configuration in the molecule and hence overlap of the π electrons of the nitrogen atom with that of the carbon atom is repressed.

Another similar case that has appeared in the current literature and one that is more closely anologous concerns the explanation offered by H. C. Brown (54) to account for the anomalous rate of reduction of t-butyl phenylketone by sodium borhydride compared to that of the homologous methyl, ethyl and isopropyl phenylketones. These authors found that the rate of reduction of these homologues was methyl phenyl ketone > ethyl phenyl ketone > isopropyl phenyl ketone. Those followed the order expected from steric and electronic considerations. However the t-butyl

phenyl ketone was found unexpectedly to reduce at a rate faster than that of the methyl phenyl ketone. This increased rate was rationalised by pointing out that there is a much lower contribution of resonance structures such as those indicated below, in the case of t-butyl phenyl ketone than in the other cases. Such resonance structures would repress the ease of reduction.



less likely resonance
structure

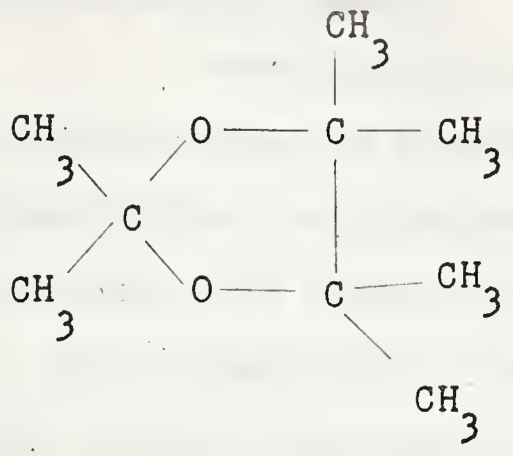


more likely resonance
structure

The main difference in the above two explanations is that the first explanation requires steric acceleration of the rate of cleavage of the C_2-O_3 bond, the ease of breakage of the C_2-O_1 being unaffected by the substituents at the C_2 and C_4 positions other than by polar effects. On the other hand, the latter explanation requires that the cleavage of the C_2-O_1 bond is retarded by steric compression between the C_2 and C_4 substituents whereas in this case the rate of cleavage of the C_2-O_3 is not affected other than by polar effects.

It should be possible to differentiate between the two explanations by a study of the rate of reduction of 2,2,4,4,5,5-hexamethyl-1,3-dioxolane whose

structure is shown below.

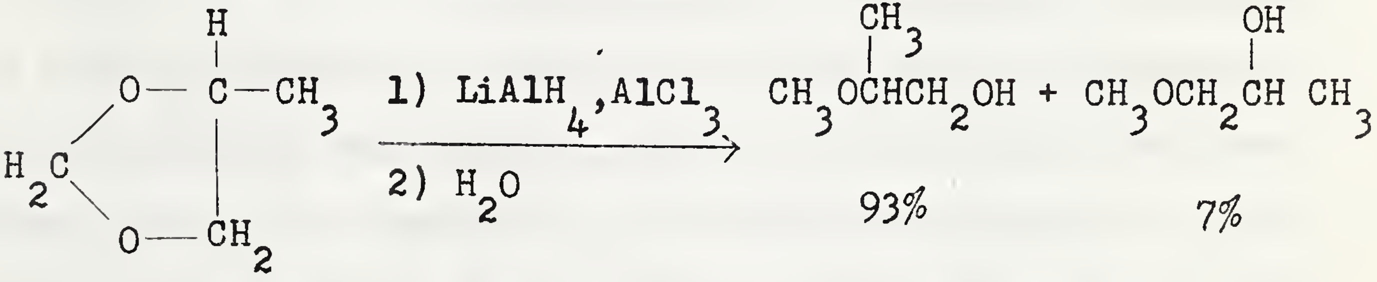


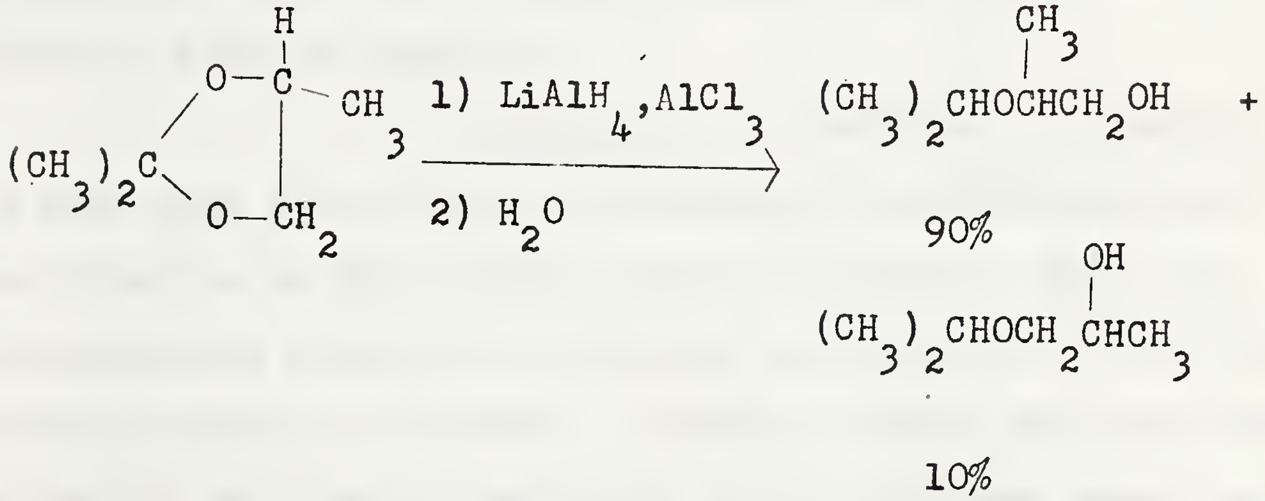
If the first explanation is correct then this dioxolane should be reduced with much greater ease than is 2,2-dimethyl-1,3-dioxolane in which there is no steric strain between the C_2 and C_4 positions. On the other hand if the latter explanation is correct then the rate of reduction of this hexasubstituted dioxolane should be greatly retarded due to steric inhibition towards the necessary coplanarity in the molecule during oxocarbonium ion formation. The ease of reduction of 2,2,4,4,5,5-hexamethyl-1,3-dioxolane has been studied and the results of this study show that its rate of reduction is greatly retarded compared to that of other 2,2-dimethyl-1,3-dioxolanes. For instance the hexamethyl dioxolane was found to be practically unchanged after being subjected to hydrogenolysis for 1 hour and even after 48 hours 30% of the recovered product was found to be unchanged starting material.

On the basis of these results the second explanation, i.e. that of steric inhibition towards oxocarbonium ion formation is preferred.

D. The Effect of Substituents at the C_2 Position upon the Direction of Ring Opening.

Substituents at the C_2 position appear to have very little effect in general upon the direction of bond breakage during the hydrogenolysis of 1,3-dioxolanes. A glance at Table VIII (Pages 70 & 71) will adequately show this. For instance with 4-methyl-1,3-dioxolane, 93% of the total product arose from the cleavage of the C_2-O_1 bond, while 2,2,4-trimethyl-1,3-dioxolane gave 90% of product which was formed by C_2-O_1 bond cleavage as the following equations demonstrate.


1) LiAlH$_4$,AlCl$_3$
2) H$_2$O
$CH_3OCH(CH_3)CH_2OH$
+
$CH_3OCH_2CH(OH)CH_3$
93%
7%


1) LiAlH$_4$,AlCl$_3$
2) H$_2$O
$(CH_3)_2CHOCH(CH_3)CH_2OH$
+
90%
$(CH_3)_2CHOCH_2CH(OH)CH_3$
10%

An attempt was made to correlate the effect of various substituents at the C_2 position upon the direction of ring opening. Towards this end the reduction of 2-substituted-4,4-dimethyl-1,3-dioxolanes was investigated. These particular compounds were chosen

to prevent the occurrence of cis-trans isomerisation in the dioxolanes. The results of this study are to be found in Table IX, Page 83. There was however little or no influence upon the direction of ring opening asserted by the C_2 substituents. The only instance where any affect was noticed was in the case of 2,2,4,4-tetramethyl-1,3-dioxolane, the possible explanations for the anomalous results obtained in this case have been discussed in the preceding section.

E. Effect of Ring Size upon the Ease of Hydrogenolysis of Cyclic Acetals and Ketals.

An observation of considerable interest is that derived from a comparison of the ease of reduction of 1,3-dioxanes and 1,3-dioxolanes, i.e. six- and five-membered rings. The results of the reductive cleavage of four 1,3-dioxanes and the corresponding 1,3-dioxolanes are to be found in Table X Page 83A.

A comparison of the ease of reduction is best made from a study of 4-methyl-1,3-dioxolane which was found to be 92% reduced within 90 minutes, while the corresponding 4-methyl-1,3-dioxane is found to be only 34% hydrogenolysed in 48 hours. A similar result was found when comparing the ease of reduction of 1,3-dioxolane which was 60% hydrogenolysed in 24 hours whilst 1,3-dioxane was reduced to the extent of only 28% within the same period.

The presence of electron-donating groups at the C_2 position was found to accelerate the hydrogenolysis of both dioxanes and dioxolanes sufficiently

TABLE IX

Investigation of the Influence of C_2-Substituents upon the Direction of Ring Opening during the Hydrogenolysis of 1,3-Dioxolanes

Expt.	Dioxolane	Reduction Products	% of Isomer in Total reduction Product
1	4,4-Dimethyl-1,3-dioxolane	1-Methoxy-2-methyl-2-propanol	8
		2-Methoxy-2-methyl-1-propanol	92
2	2,4,4-Trimethyl-1,3-dioxolane	1-Ethoxy-2-methyl-2-propanol	10
		2-Ethoxy-2-methyl-1-propanol	90
3	4,4-Dimethyl-2-phenyl-1,3-dioxolane	1-Benzyloxy-2-methyl-2-propanol	11
		2-Benzyloxy-2-methyl-1-propanol	89
4	2,2,4,4-Tetramethyl-1,3-dioxolane	1-*iso*Propoxy-2-methyl-2-propanol	94
		2-*iso*Propoxy-2-methyl-1-propanol	6

TABLE X

A Study of the Relative Ease of Reduction of 1,3-Dioxanes and 1,3-Dioxolanes with Lithium Aluminum Hydride and Aluminium Chloride

Expt.	Dioxane or Dioxolane	Reduction Time (hr)	Total Recovery %[a]	% yield of starting material[b]	% yield of reduction products[b]
1	1,3-Dioxolane	24	55	40	60
2	1,3-Dioxane	24	75	72	28
3	4-Methyl-1,3-dioxolane	1.5	85	8	92
4	4-Methyl-1,3-dioxane	48	86	66	34[c]
5	2-Phenyl-1,3-dioxolane	1.0	70	0	100
6	2-Phenyl-1,3-dioxane	1.0	63	0	100
7	2,2,4-Trimethyl-1,3-dioxolane	1.5	86	0	100
8	2,2,4-Trimethyl-1,3-dioxane	1.5	84	0	100[d]

[a] Total recovery includes both reduction products and recovered starting materials

[b] Percent yields of materials based upon total recovery

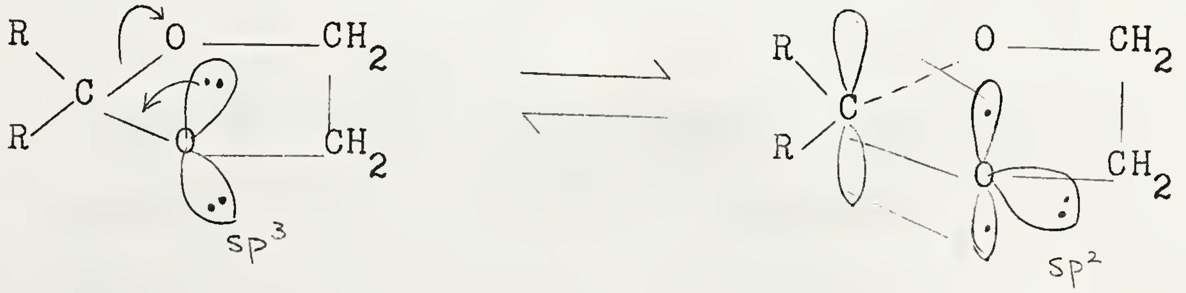
[c] Reduction product consisted of 3-methoxy-1-butanol (92%) and 1-methoxy-3-butanol (8%).

[d] Reduction product consisted of 3-*iso*propoxy-1-butanol (87%) and 1-*iso*propoxy-3-butanol (13%).

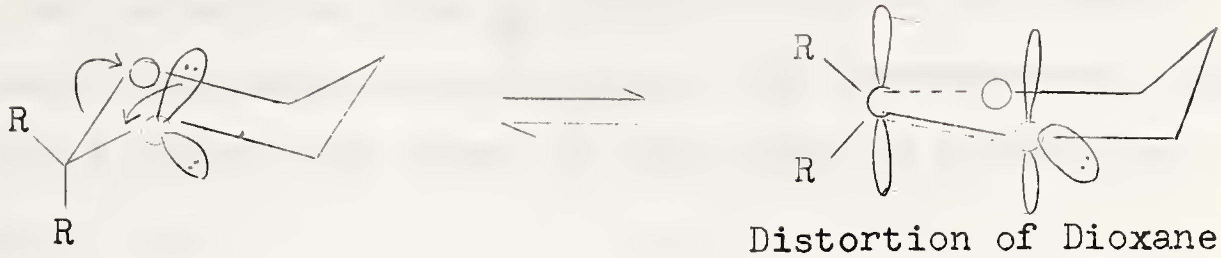
so that both the five- and six-membered rings were reduced completely within 90 minutes.

Apparently the six-membered cyclic acetals and ketals are reduced more slowly than the corresponding five-membered cyclic compounds. The strong evidence that has been found that ring cleavage to form the transient oxocarbonium ion is part of the rate-controlling step in the reductive cleavage of acetals and ketals can be well supported by these observations.

The incipient formation of the oxocarbonium ion by ring cleavage requires that the C_2-O-C grouping attains co-planarity for optimum results. This coplanar configuration can be brought about more readily in the five-membered ring system, which is nearly coplanar initially (55), than in the six-membered dioxane ring. In the latter case there must occur first a modification of the normal chair (or boat) structure to permit effective stabilisation of oxocarbonium ion by overlap of the π electrons of the oxygen atom with the developing empty orbital of the C_2 atom. The following structures will serve to illustrate the point.

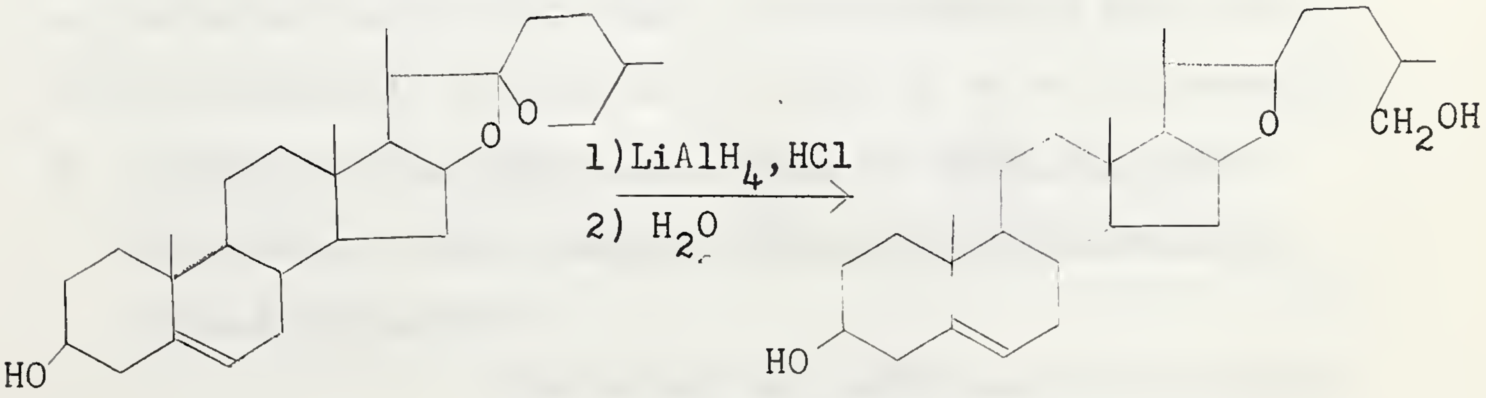


Little distortion of ring required during oxocarbonium ion formation

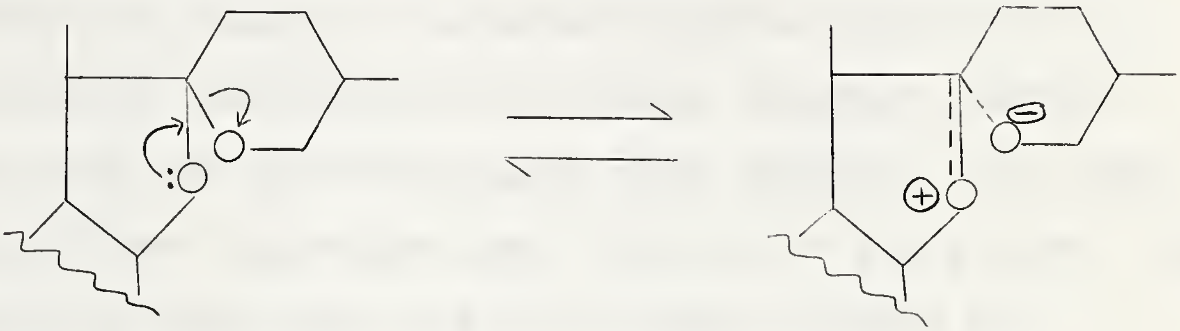


Distortion of Dioxane ring required for formation of oxocarbonium ion

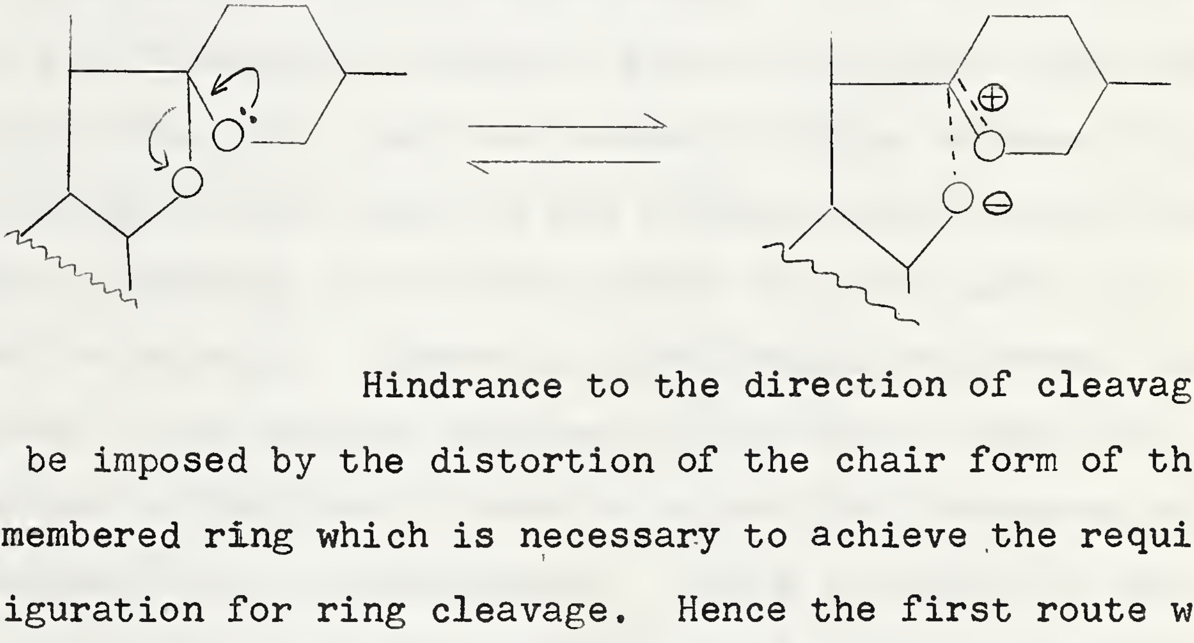
During the formation of the oxocarbonium ion by cleavage of the 1,3-dioxane ring, the normal chair form of the ring must become distorted in order to assume the configuration required to produce cleavage of the ring. This distortion will impose hindrance to oxocarbonium ion formation and hence cause retardation in the rate of reduction of 1,3-dioxanes compared to that of the corresponding 1,3-dioxolanes where overlap of the π electrons of the oxygen atom with the C_2 carbon imposed little or no strain upon the molecule. Further support for this explanation is to be found in the results of Doukas and Fontaine (1) who found that when diosgenin was hydrogenolysed, by lithium aluminum hydride in the presence of acids, only the six-membered ring was cleaved, the five-membered ring remaining intact as shown by the following equation.



The driving force behind the cleavage of the six-membered ring of diosgenin will be the overlap of the π electrons of the oxygen of the five-membered ring with the carbon atom common to both rings as illustrated below



This state of affairs will be easier to achieve than in the alternative route of cleavage as shown below.



Hindrance to the direction of cleavage will be imposed by the distortion of the chair form of the six-membered ring which is necessary to achieve the required configuration for ring cleavage. Hence the first route will be preferred and in this case the six-membered ring would be preferentially cleaved as is found to be so in actuality.

F. A Study of the Effect of Change of Lewis Acid upon Direction of Ring Opening During the Hydrogenolysis of 1,3-Dioxolanes.

This study was performed in an attempt

to determine whether or not the relative amounts of C_2-O_1 and C_2-O_3 bond opening during the hydrogenolysis of asymmetrical dioxolanes was dependent upon the Lewis acid used to promote the reduction. Accordingly a series of reductions performed upon 2,2,4-trimethyl-1,3-dioxolane was carried out using both aluminum chloride and boron trifluoride in combination with lithium aluminum hydride. Apart from the differing Lewis acids employed, the conditions of each experiment were the same in every case. The results of this study are to be found in Table XI.

Apparently the Lewis acid plays no part in determining the direction of ring opening during the hydrogenolysis of 1,3-dioxolanes. If any effects due to the difference in molecular size of the Lewis acid play a significant part then the results of these effects should be noticed in this study as the aluminum chloride molecule could be expected to be much bulkier than the boron trifluoride molecule. However no distinction whatsoever can be made in the results obtained by the use of boron trifluoride or aluminum chloride to effect the hydrogenolysis of asymmetrical 1,3-dioxolanes. Hence it should be safe to conclude that steric inhibition to the approach of the Lewis acid to the co-ordination site of the dioxolane ring is negligible and plays little or no part in determining the direction of ring opening during hydrogenolysis.

G. Concerning the Hydrogenolysis of *cis* and *trans* Isomers of 2,4-Disubstituted-1,3-Dioxolanes.

From a consideration of the geometry

TABLE XI

Study of the Effect on Direction of Ring Opening in Going from Aluminum Chloride to Boron Trifluoride as the Lewis Acid employed in the Hydrogenolysis of 2,2,4-Trimethyl-1,3-Dioxolane [a]

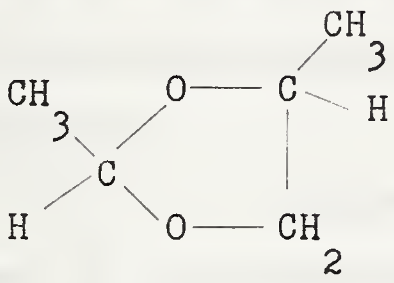
Expt.	Lewis Acid	Total Yield %	2-*iso*Propoxy-1-propanol [b]	1-*iso*Propoxy-2-propanol [b]
1	$AlCl_3$	76	81.5	18.5
2	$AlCl_3$	81	82	18
3	BF_3	75 [c]	82.5	17.5
4	BF_3	75 [c]	82	18

a The time for each reduction was 90 minutes.

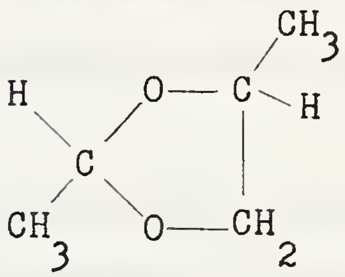
b Percentages based upon total yield.

c A small amount of unchanged starting material was found in the product.

of the 1,3-dioxolane molecule it may be seen that cis-trans isomerism can be exhibited by dioxolanes possessing substituents at the C_2 and C_4 positions. Cis-trans isomerism can also be exhibited by 4,5-disubstituted (56) and 2,4,5-trisubstituted-1,3-dioxolanes (56). However this study has been confined to the cis and trans isomers of 2,4-disubstituted-1,3-dioxolanes. The structures of the respective isomers are illustrated here using as an example 2,4-dimethyl-1,3-dioxolane.



cis



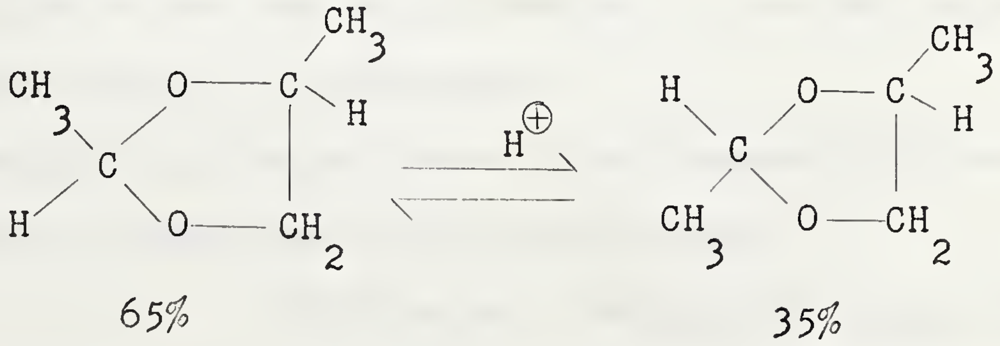
trans

The separation of the isomers of 2,4-dimethyl-1,3-dioxolanes, the simplest molecule of the type under discussion, was first achieved by Lucas and Guthrie (57) by fractionnal distillation of the equilibrium mixture of the isomers obtained by the acid-catalysed transacetalation of acetaldehyde diamylacetal and 1,2-propanediol. These workers obtained two fractions, one which boiled at 90.1° and another which had a boiling point of 93.0°, but they did not assign a configuration to either of the isomers.

Barker and co-workers (58) have also managed to isolate the two isomers of 2,4-dimethyl-1,3-

dioxolane by means of fractionnal distillation of the equilibrium mixture of the isomers. These workers assigned to the lower boiling isomer, b.p. 89.7°, the cis configuration and to the higher boiling isomer, b.p. 93.5°, the trans structure. The rationnale behind their assignment of configuration followed from the work of Haresnape (59) and Birch and Dean (60). Haresnape (59), from a purely theorectical standpoint, reviewed the problem of the cis and trans isomers of 1,3-dimethylcyclopentane. The rationnale of Haresnape was confirmed by the later work of Birch and Dean (60) who unambiguously synthesised the two isomers of this compound.

Barker and co-workers (58) based their assignment of configuration of the isomers of 2,4-dimethyl-1,3-dioxolane by analogy with the 1,3-dimethylcyclopentanes, as the 1,3-dioxolane molecule shows a marked geometrical resemblance to the cyclopentane molecule. These workers also found by means of vapour phase chromatography that in the equilibrium mixture of the isomers, the cis isomer is present to the extent of 65% and the trans isomer to the extent of 35%.



From the ratio of the isomers present at their equilibrium concentrations it can be seen that the cis isomer is slightly more stable than the trans isomer.

The study of the hydrogenolysis of 1,3-dioxolanes with lithium aluminum hydride and aluminum chloride has shown that 1,3-dioxolanes capable of exhibiting cis-trans isomerisation yielded varying ratios of products afforded by either C_2-O_3 or C_2-O_1 bond cleavage depending upon the amounts of each isomer present in the starting material. Consequently it was thought to be of interest to study the hydrogenolysis of the separate isomers to gain a better understanding of the factors governing the direction of ring opening during reduction of 1,3-dioxolanes.

With this object in view pure samples of cis-and trans-2,4-dimethyl-1,3-dioxolane and also cis-and trans-2-ethyl-4-methyl-1,3-dioxolane were prepared and a study of their hydrogenolysis undertaken in an effort to clarify the following points.

i) To what extent do the cis and trans isomers differ in the amounts of each reduction product afforded upon this hydrogenolysis.

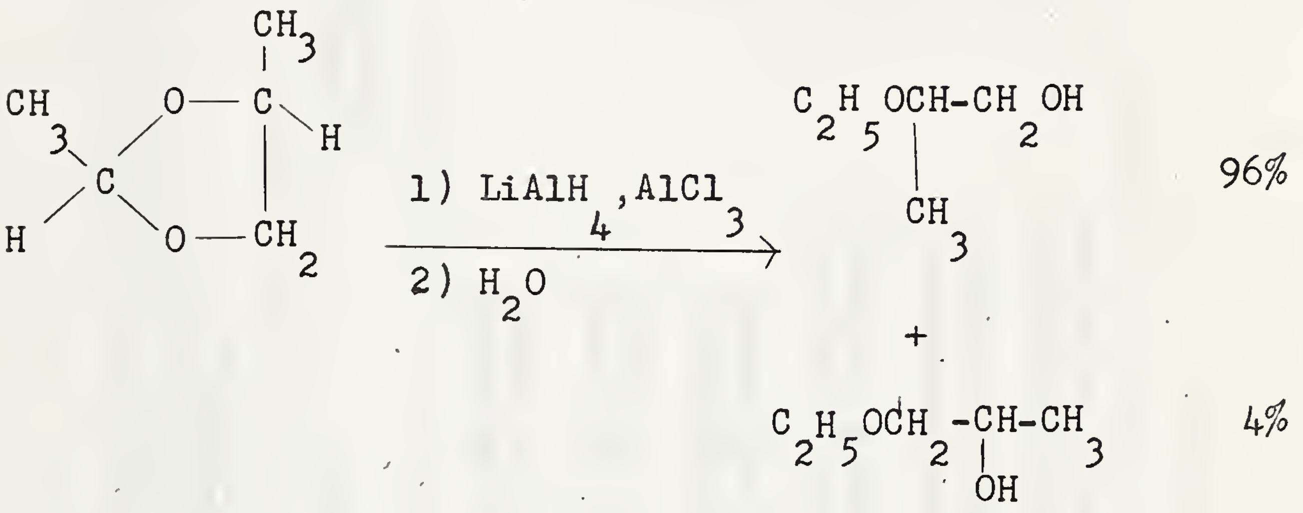
ii) Whether or not any equilibration of the particular isomer occurs during the reduction.

and finally iii) Whether there is any marked difference in the rates of reduction of the two isomers.

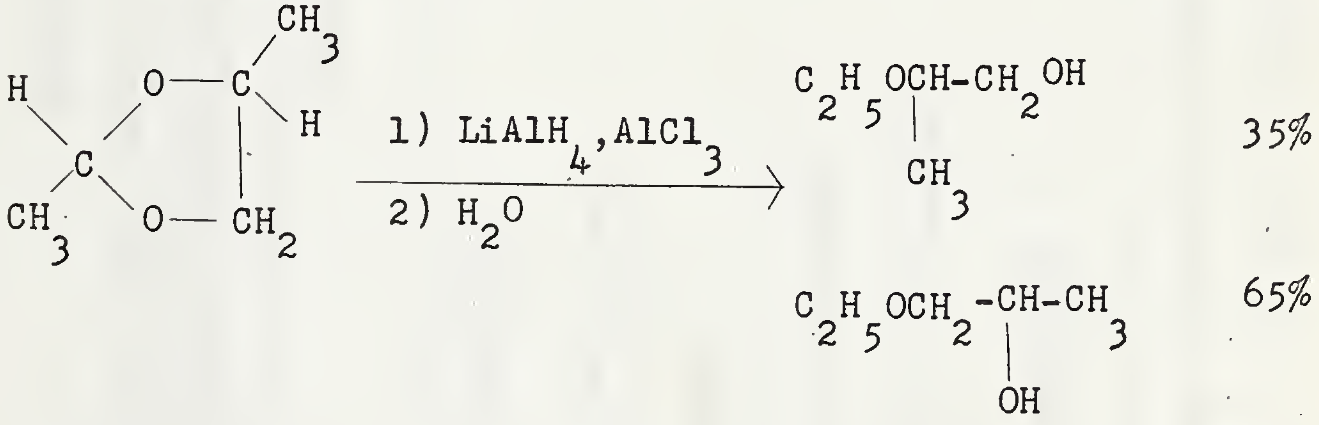
To this end, the cis and trans isomers of 2,4-dimethyl-1,3-dioxolane and 2-ethyl-4-methyl-1,3-dioxolane were subjected to hydrogenolysis by lithium aluminum

hydride and aluminum chloride. The results of this study are to be found in Table XII, Page 93.

These results show that the cis isomer of both of these dioxolanes affords predominantly C_2-O_1 bond cleavage to yield the primary alcohol as illustrated.


1) LiAlH$_4$, AlCl$_3$
2) H$_2$O
$C_2H_5OCH(CH_3)$-CH_2OH
96%
+
$C_2H_5OCH_2$-$CH(OH)$-CH_3
4%

However in the corresponding trans isomers C_2-O_3 bond cleavage is slightly favoured over C_2-O_1 bond cleavage as shown by the following example.


1) LiAlH$_4$, AlCl$_3$
2) H$_2$O
$C_2H_5OCH(CH_3)$-CH_2OH
35%
$C_2H_5OCH_2$-$CH(OH)$-CH_3
65%

The possibility that the results shown in Table XII Page 93, may not afford a true picture as to the extent of preferential bond cleavage of the respective isomers, due to the occurrence of simultaneous isomerisation of the materials induced by the aluminum chloride was taken into consideration. It is well known that the

TABLE XII

The Hydrogenolysis of *cis* and *trans* isomers of 2,4-Disubstituted-1,3-Dioxolanes by Lithium Aluminum Hydride and Aluminum Chloride[a]

Expt.	Dioxolane	Reduction Products	% of each Constituent in Reduction Product
1	*cis*-2,4-Dimethyl-1,3-dioxolane	1-Ethoxy-2-propanol	4
		2-Ethoxy-1-propanol	96
2	*trans*-2,4-Dimethyl-1,3-dioxolane	1-Ethoxy-2-propanol	65
		2-Ethoxy-1-propanol	35
3	2,4-Dimethyl-1,3-dioxolane[b]	1-Ethoxy-2-propanol	24
		2-Ethoxy-1-propanol	76
4	*cis*-2-Ethyl-4-methyl-1,3-dioxolane	1-*n*-Propoxy-2-propanol	6
		2-*n*-Propoxy-1-propanol	94
5	*trans*-2-Ethyl-4-methyl-1,3-dioxolane	1-*n*-Propoxy-2-propanol	67
		2-*n*-Propoxy-1-propanol	33
6	2-Ethyl-4-methyl-1,3-dioxolane[b]	1-*n*-Propoxy-2-propanol	32
		2-*n*-Propoxy-1-propanol	68

[a] Each Hydrogenolysis was allowed to proceed for 60 minutes.

[b] Equilibrium mixtures of the *cis* and *trans* isomers.

equilibration of 1,3-dioxolanes is promoted by Lewis acids (58). Indeed we have found that cis-2,4-dimethyl-1,3-dioxolane is completely equilibrated in a few hours at room temperature by a catalystic amount of aluminum chloride in ether solution.

To investigage the possibility of this occurring during hydrogenolysis, a series of partial reductions was carried out on both the cis and the trans isomers of 2,4-dimethyl-1,3-dioxolane. The total recovered product from these reductions was then analysed, by means of v.p.c. for both of the expected reduction products and also to determine the constitution of the recovered dioxolane and hence to find out whether or not partial equilibration of the isomers does occur simultaneously with the hydrogenolysis. The results of this study are to be found in Table XIII, Page 95.

The results show that as the reduction of the cis isomer nears completion a small amount of equilibration occurs as evidenced by the presence of both cis and trans isomers in the recovered starting material. In the case of the trans isomer, no partial equilibration was observed as none of the cis isomer was found to be present in the recovered starting material of any of the experiments.

These observations may be rationalised by either of the following explanations.

i) That no isomerisation of the trans isomer, but that isomerisation of the cis isomer, does occur during their respective hydrogenolysis. This seems rather dubious as

TABLE XIII

Partial Reductions of *cis* and *trans* isomers of 2,4-Dimethyl-1,3-dioxolane[a]

Expt.	Moles Dioxolane	Moles $LiAlH_4$	Moles $AlCl_3$	% Ratio of Reduction Products[b]		Whether equilibration observed in recovered starting material
				A	B	
			Trans-2,4-Dimethyl-1,3-dioxolane			
1.	0.05	0.01	0.005	37	63	NO
2.	0.05	0.01	0.01	33	67	NO
3.	0.05	0.025	0.02	33	67	NO
			Cis-2,4-Dimethyl-1,3-dioxolane			
4.	0.05	0.01	0.005	96	4	NO
5.	0.05	0.02	0.015	96	4	NO
6.	0.05	0.025	0.02	96	4	TRACE
7.	0.05	0.035	0.03	96	4	TRACE +

[a] The reaction time was 30 minutes in all cases. The total recovery was of the order of 80% in all cases.

[b] Reduction Product *A* is 2-Ethoxy-1-propanol. Reduction product *B* is 1-Ethoxy-2-propanol.

the *cis* isomer is found to be somewhat more stable than the *trans* isomer.

ii) That a small amount of equilibration accompanies the hydrogenolysis of each of the isomers, but the *cis* isomer is more rapidly reduced than the *trans* isomer and therefore its presence cannot be detected in the starting material recovered from the reduction of the *trans* isomer under the conditions of limited reduction employed.

The second of these explanations was established as the preferred one by studying the *relative* rates of reduction of the two isomers. No *absolute* rate studies on the hydrogenolysis of the isomers were carried out due to the failure to find a satisfactory method (instrumental or otherwise) of following the reaction *in situ*. An accurate study of the *absolute* rates of hydrogenolysis by quantitative measurement of the rate of formation of the products or of disappearance of the starting materials was also considered to be impractical due to the loss of each material that would be incurred during the work-up of the reaction mixture.

However, due to the vastly different proportions of the two materials obtained on reduction of the two isomers, it was found possible to obtain the approximate *relative* rates of reduction of the *cis* and *trans* isomers of 2,4-dimethyl-1,3-dioxolane by a study of the ratios of the two products obtained by a partial reduction of a mixture of the two isomers.

The rationale behind the study of the

relative rates of hydrogenolysis of mixtures of 1,3-dioxolanes by competitive reduction has been given previously on Page 63. However in the case under discussion here, the products afforded by both the *cis* and the *trans* isomers undergoing parallel reductions are identical but are produced in different proportions by the two isomers. We have seen earlier in this section that *cis*-2,4-dimethyl-1,3-dioxolane affords 96% of 2-ethoxy-1-propanol and 4% of 1-ethoxy-2-propanol upon hydrogenolysis whereas *trans*-2,4-dimethyl-1,3-dioxolane gives 35% of 2-ethoxy-1-propanol and 65% of 1-ethoxy-2-propanol. Therefore, if, in a competitive reduction, x moles of the *cis* isomer are reduced for every mole of *trans* isomer reduced then the ratio of 2-ethoxy-1-propanol to 1-ethoxy-2-propanol afforded will be given by,

2-Ethoxy-1-propanol : 1-ethoxy-2-propanol = $(96x+35):(4x+65)$ (i)

Hence from a consideration of the respective amounts of the two isomers initially present in the material subjected to reduction, both x and the relative rate of reduction of the *cis* and *trans* isomers may be calculated directly from the percentage composition of the two alcohols comprising the reduction product. The results of this study are to be found in Table XIV Page 98.

These results show that the *cis* isomer of 2,4-dimethyl-1,3-dioxolane is reduced 6.8 times faster than the corresponding *trans* isomer. This observation was also confirmed by the fact that during the partial

TABLE XIV

A Study of the Relative Rates of Hydrogenolysis of the *cis* and *trans* isomers of 2,4-Dimethyl-1,3-Dioxolane with Lithium Aluminum Hydride and Aluminum Chloride

Expt.	Ratio of *cis*:*trans* isomers in starting material	Composition of Reduction Product		x [a]	Relative rate of Reduction of *cis* isomer (*trans*=1) [b]
1	50% *cis*, 50% *trans*	1-Ethoxy-2-propanol 2-Ethoxy-1-propanol	11% 89%	7.7	7.7
2	50% *cis*, 50% *trans*	1-Ethoxy-2-propanol 2-Ethoxy-1-propanol	12% 88%	6.6	6.6
3	65% *cis*, 35% *trans*	1-Ethoxy-2-propanol 2-Ethoxy-1-propanol	9% 91%	11.2	6.1
4	35% *cis*, 65% *trans*	1-Ethoxy-2-propanol 2-Ethoxy-1-propanol	17% 83%	3.7	6.9

a *x* is the ratio of moles of *cis*-isomer to moles of *trans* isomer reduced, calculated from equation (i) Page 97.

b Average relative rate of *cis*-2,4-dimethyl-1,3-dioxolane calculated from Expts 1-4 is 6.8 times that of *trans*-2,4-dimethyl-1,3-dioxolane.

reduction of an equimolar mixture of the *cis* and *trans* isomers of this material, the amount of the *cis* isomer remaining in the unchanged starting material after reduction was diminished to a far greater extent than was the *trans* isomer.

Similar studies upon the relative rates of hydrogenolysis of the *cis* and *trans* isomers of 2-ethyl-4-methyl-1,3-dioxolane showed the *cis* isomer to be reduced approximately ten times faster than the *trans* isomer.

The observation that the *cis* isomers are reduced faster than the corresponding *trans* isomers is somewhat surprising in view of the fact that the *cis* isomer is the more stable of the two isomers, being present to the extent of 65% in an equilibrium mixture of the two isomers in the case of 2,4-dimethyl-1,3-dioxolane. However this result agrees with the findings of Salomaa (61) who found that *cis*-2,4-dimethyl-1,3-dioxolane is *hydrolysed* approximately *four* times faster than the *trans* isomer in an acidic medium.

Any plausible explanation of these results will have to account for,

(a) The different proportions of products obtained on hydrogenolysis of the *cis* and *trans* isomers of 2,4-dimethyl-, and 2-ethyl-4-methyl-1,3-dioxolane.

(b) The enhanced rate of hydrogenolysis and also that of acid catalysed hydrolysis (61), of the *cis* isomers over that of the corresponding *trans*-1,3-dioxolanes.

If we consider the ratios of hydrogenolysis products afforded by the *cis* isomer we can see that

the ratio of C_2-O_1 to C_2-O_3 bond cleavage is comparable with that of other 1,3-dioxolanes containing electron donating substituents at the C_4 position. For instance 2,2,4-trimethyl-1,3-dioxolane and 2,4,4-trimethyl-1,3-dioxolane afford 90% and 92% of C_2-O_1 bond cleavage respectively upon hydrogenolysis, which is in good agreement with the 96% of C_2-O_1 bond cleavage found in the case of cis-2,4-dimethyl-1,3-dioxolane. Hence we may regard the results of hydrogenolysis of the cis isomers to be normal, and those results of reduction of the trans isomers to be abnormal. Therefore it may be reasoned that the rates of reduction of the cis isomers can be regarded to be the expected rates and those of the trans isomers to be retarded to a certain degree.

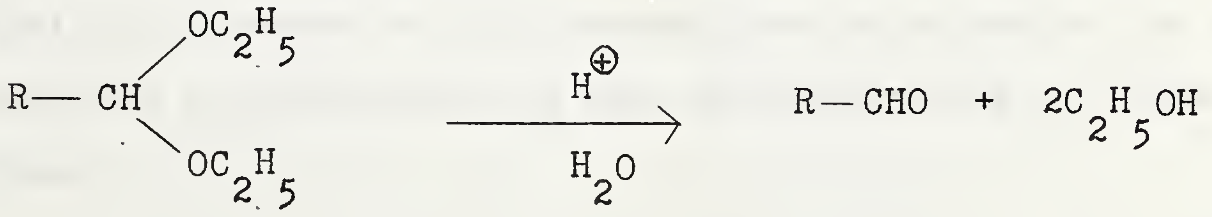
A continuation of the above line of reasoning will give rise to the possibility that this retardation in the rate of hydrogenolysis and hydrolysis occurs at the C_2-O_1 bond. If the rate of cleavage of this bond is inhibited by certain effects then the molecule will be retarded in its reduction or hydrolysis and the amount of reduction product afforded by cleavage of this bond will be reduced, and hence a corresponding increase in the amount of product afforded by C_2-O_3 bond cleavage can be expected.

No satisfactory explanation as to why C_2-O_1 bond cleavage should be retarded can be offered at this stage.

CONCLUSIONS

A final analysis of the results obtained in this study reveals a striking similarity between these results and of those cited by the many workers who have investigated the acid-catalysed hydrolysis of acetals and ketals.

Most of the studies appearing in the literature refer to the effect of substituents in the central carbon atom of acyclic acetals and ketals, i.e. the carbon atom corresponding to the C_2 atom of the 1,3-dioxolane and 1,3-dioxane rings. Kreevoy and Taft (62) conducted an intensive survey of the effect of substituents upon the rate of acid-catalysed hydrolysis of diethyl acetals and ketals. They found that polar and resonance effects had a greater bearing upon the rate of hydrolysis than did steric factors. They also found that the rate of hydrolysis of acetals and ketals increased according to the electron donating capacity of the substituent R in the following equation.



$$R-CH(OC_2H_5)_2 \xrightarrow[H_2O]{H^{\oplus}} R-CHO + 2C_2H_5OH$$

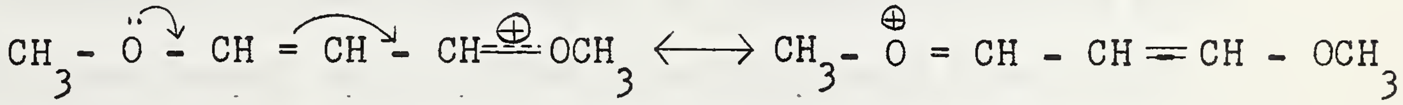
The rates of hydrolysis were of the following order.

$R = \alpha\beta$-unsaturated $\gg C_6H_5- > $ alkyl- $\gg$ formals $> CH_2Cl-$.

This correlation of substituent effects upon the rate of hydrolysis of acetals corresponds very well with the results found in the present study upon the hydrogenolysis of acetals and ketals. Our results show that the rate of reduction is enhanced by the presence of electron-donating substituents at the C_2 or C_4 positions of the dioxolane or dioxane ring, and that a corresponding retardation in the rate occurs when electron-withdrawing substituents are present at these positions.

The observation, of Kreevoy and Taft, that $\alpha\beta$-unsaturated acetals were hydrolysed much more readily than were other acetals prompted us to investigate the ease of hydrogenolysis of this type of acetal. Accordingly the reduction of 1,3,3-trimethoxy-1-propene was undertaken. This acetal was found to be hydrogenolysed by lithium aluminum hydride alone, the presence of a Lewis acid, so necessary to promote hydrogenolysis in acetals and ketals, was not required in this case.

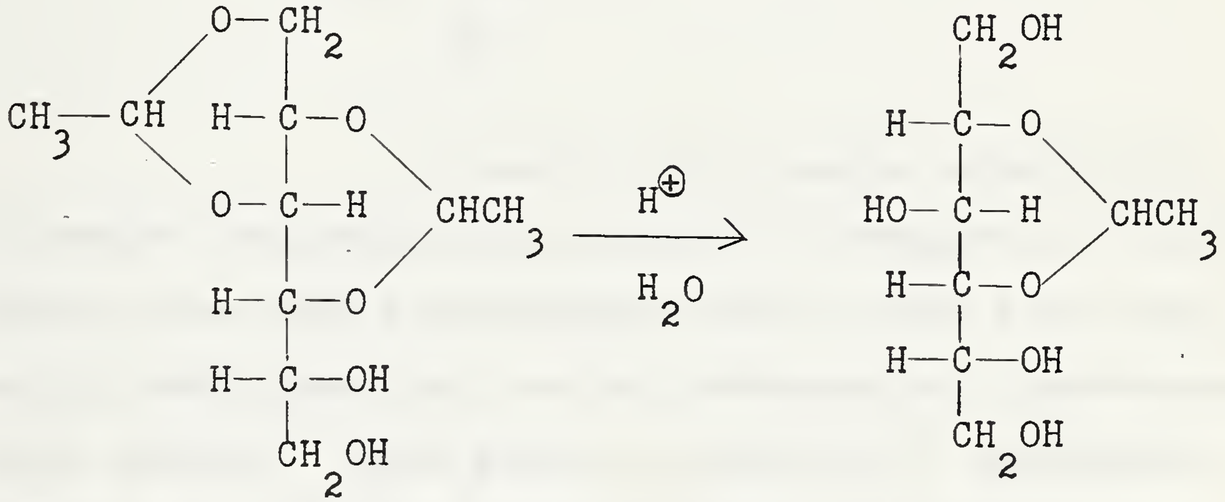
This greater ease of reduction of an $\alpha\beta$-unsaturated acetal may be attributed to the greater stability afforded to the intermediate oxocarbonium ion by resonance contributions via the $\alpha\beta$-double bond as illustrated.



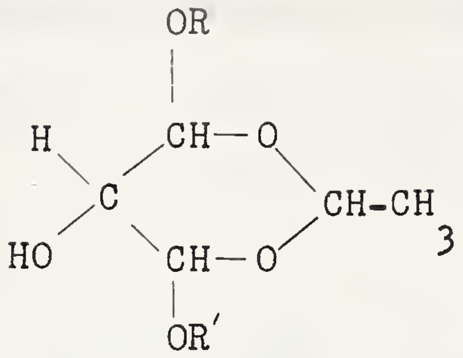
$$CH_3-\ddot{O}-CH=CH-CH\overset{\oplus}{=}OCH_3 \longleftrightarrow CH_3-\overset{\oplus}{O}=CH-CH=CH-OCH_3$$

Salomaa (61) has shown that cis-2,4-dimethyl-1,3-dioxolane is hydrolysed approximately four times faster than the corresponding trans isomer in aqueous acid medium. This figure is in good agreement with the factor of approximately six by which the cis-2,4-dimethyl-1,3-dioxolane was found to be reduced faster than the trans isomer.

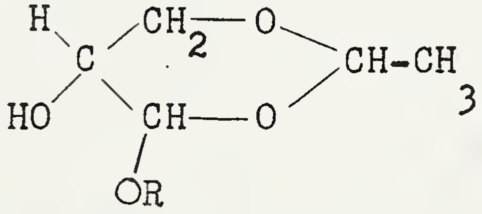
The similarity between rates of hydrolysis and hydrogenolysis of acetals and ketals may also be found in carbohydrate chemistry. Hexitol acetals which span primary and secondary positions are found to be hydrolysed preferentially over acetals formed from two secondary hydroxylic groups as the following example (63) illustrates.



The preferential hydrolysis of the 1,3-ethylidene acetal of 1,3:2,4-diethylidenesorbitol may be attributed to the retardation of hydrolysis of the 2,4-ethylidene acetal by the electron-withdrawing groups at both the C_4 and C_6 positions of the 1,3-dioxane ring as shown in the following structure.

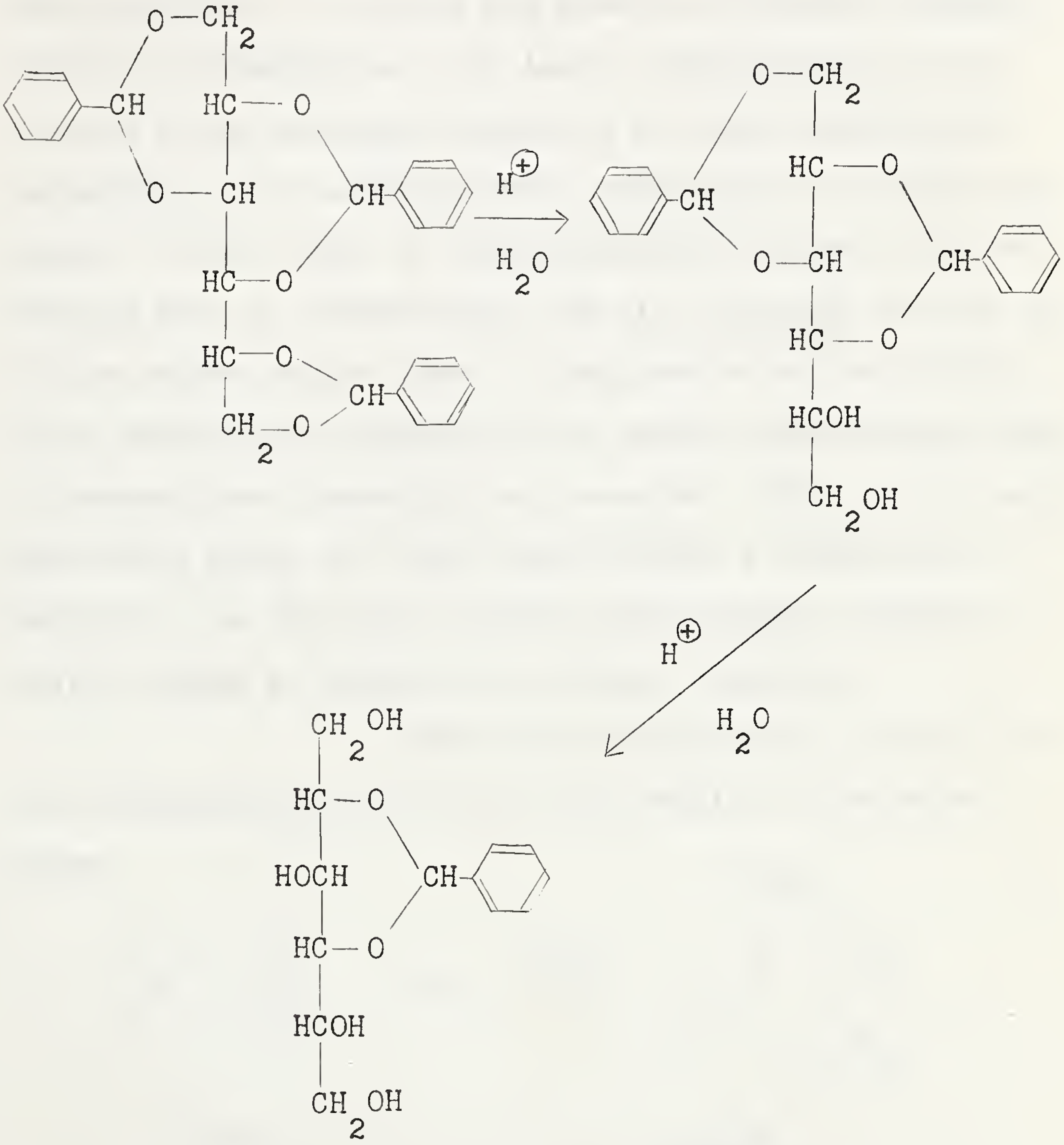


Whereas the 1,3-ethylidene acetal lacks the second retarding group at the C_6 position of the 1,3-dioxane ring and is therefore hydrolysed preferentially.



A study of the results cited in the literature concerning the preferential hydrolysis of cyclic acetals shows that five-membered cyclic acetals are more readily hydrolysed than are the corresponding six-membered cyclic acetals. Once again by resorting to carbohydrate chemistry one can find many examples to illustrate this point. For instance, 1,3:2,4:5,6-tribenzylidenesorbitol upon graded acidic hydrolysis (64) gives initially 1,3:2,4-dibenzylidenesoribitol and then 2,4-benzylidenesorbitol thus illustrating that the five-membered cyclic acetal is cleaved more readily than the six-membered cyclic acetal formed from a primary and secondary hydroxyl group. The

six-membered cyclic acetal formed from two secondary hydroxyl groups being the most resistant to hydrolysis is shown by the following scheme.

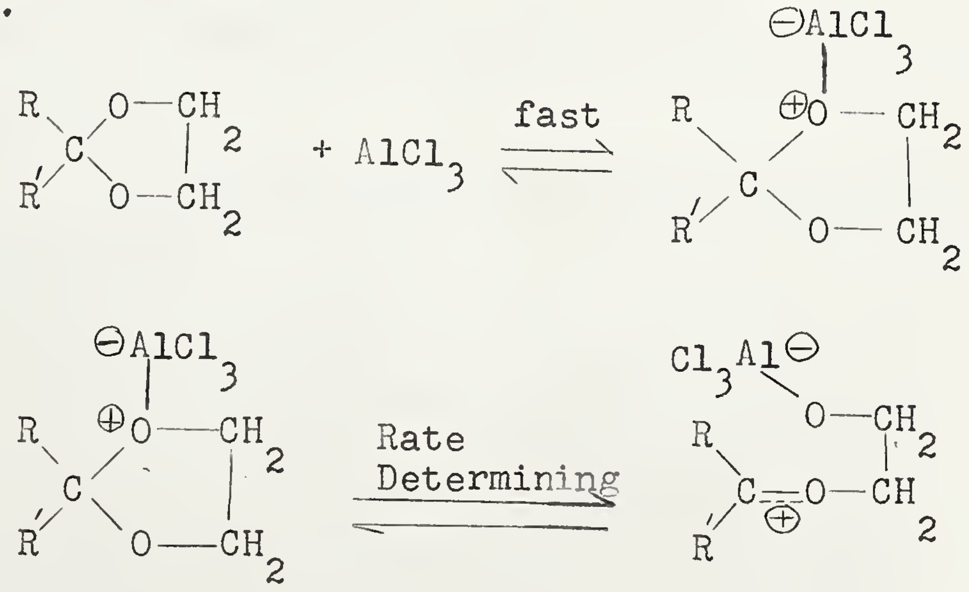


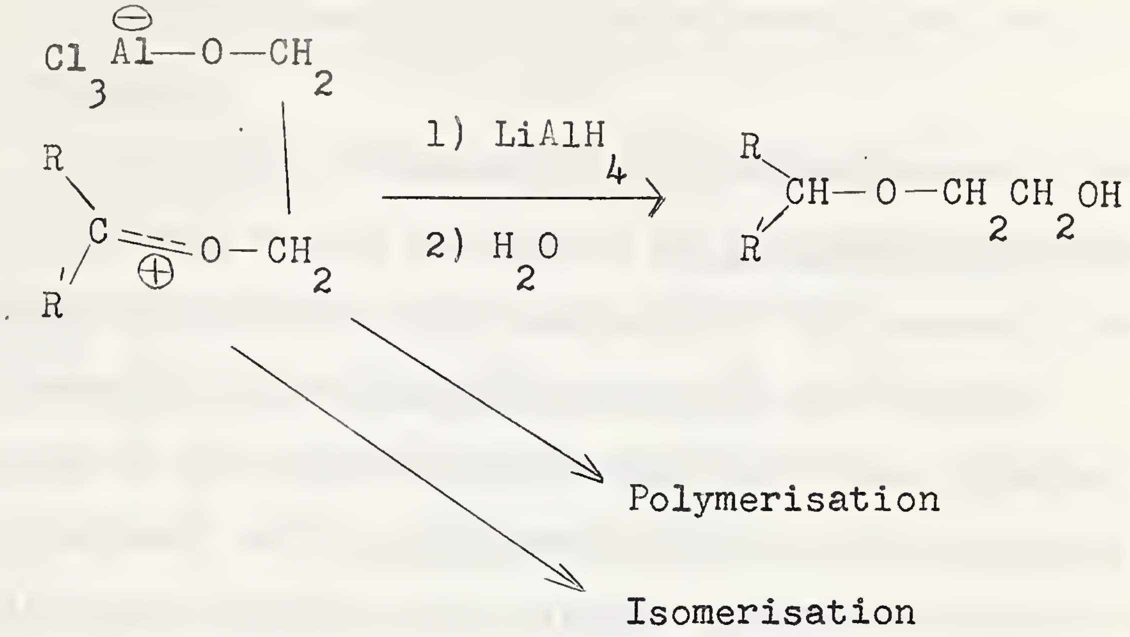
The preferential cleavage of five-membered cyclic acetals over the six-membered cyclic acetals has been rationallised on Pages 82-5 of this thesis.

On the basis of the many similarities

to be found in the literature between the hydrolysis of acetals and ketals and the results obtained during the course of this study we feel that the mechanism of the hydrogenolysis of acetals and ketals by lithium aluminum hydride in combination with Lewis acids may best be explained by an anologous scheme to the well-established mechanism of the acid-catalysed hydrolysis of acetals and ketals. In the case of hydrogenolysis, however, the reduction step is irreversible and also cleavage of only one of the carbon-oxygen bonds is obtained since the driving force behind the breaking of the second carbon-oxygen bond is missing once reduction has occurred. This is not so in hydrolysis where the first step affords a hemiacetal or hemiketal, in which the second carbon-oxygen linkage is easily broken to afford the carbonyl compound.

The proposed mechanistic scheme for the hydrogenolysis of acetals and ketals is presented below.





Cl3 Al—O—CH2
R
C
O—CH2
R
1) LiAlH4
2) H2O
R
CH—O—CH2CH2OH
R
Polymerisation
Isomerisation

BRIEF SUMMARY OF RESULTS

The hydrogenolysis of cyclic acetals and ketals has been studied.

During the hydrogenolysis of hemithioacetals and hemithioketals it was found that only carbon-oxygen bond cleavage occurred. No hydrogenolysis of dithioacetals and dithioketals was obtained. Explanations for the non-cleavage of the carbon-sulphur bond have been offered.

The study of the hydrogenolysis of 1,3-dioxolanes and 1,3-dioxanes revealed that electron-donating groups at the C_2 and C_4 positions enhanced the ease of hydrogenolysis whereas electron-withdrawing groups rendered hydrogenolysis less facile when present at these positions.

Electron-donating groups at the C_4 position of the dioxolane or dioxane ring directed ring opening at the C_2-O_1 bond whereas electron-withdrawing groups at this position promoted cleavage of the C_2-O_3 bond.

Five-membered cyclic acetals were found to be more readily hydrogenolysed than the corresponding six-membered compounds.

Explanations have been offered to account for these observations.

EXPERIMENTAL.

All boiling points and melting points recorded in the following pages are uncorrected.

Except where otherwise stated, all g.l.c. analyses were done with a Burrell K-2 Kromo-Tog apparatus using a 2-metre column packed with 25% of carbowax 20M on Gas-Chrom P as the solid stationary phase. Helium, at a flow-rate of approximately 80 ml. per minute was the carrier gas. The column temperature was dependent upon the boiling point of the compounds being analysed. All compounds were identified by comparison of their g.l.c. retention times with those of authentic samples. Quantitative analyses were made by measuring the integrated areas of the peaks concerned. These areas were compared with those of peaks obtained by use of definite measured amounts of samples.

Infra-red spectra were recorded in a Perkin-Elmer model 221 instrument. Nuclear magnetic resonance spectra were recorded with a Varian Associates A-60 spectrometer.

PART A Experimental Work Concerned with the Study of the Reductive Cleavage of Hemithioacetals and Ketals.

1. Preparation of Starting Materials.

2-Mercaptoethanol was obtained as a commercial product from Eastman Kodak Co. Inc., New York.

1,2-Dimercaptoethane was obtained as a commercial product from Wateree Chemical Co. Inc., Lugoff, S. Carolina.

2-Mercaptopropane was obtained commercially from Eastman Kodak Co. Inc., New York.

1,2-Dimercaptopropane was prepared by the method described by Culvenor et al.(65) as follows:

Carbon disulphide (228 g., 3.0 mole) was added slowly to a cooled and stirred solution of potassium hydroxide (140 g., 2.5 mole) in methanol (450 ml.). During the addition a precipitate of potassium methyl xanthate slowly appeared. After complete addition of the carbon disulphide the reaction mixture was stirred and cooled in ice whilst propylene oxide (58 g., 1.0 mole) was added at such a rate that the temperature of the reaction mixture did not exceed 30°. The reaction mixture was allowed to stand at 25° for 8 hours and then poured into 3l. of cold water. The resulting oil was isolated by ether extraction, and dried over magnesium sulphate. Removal of the solvent by distillation afforded 130 g. (87%) of propylene trithiocarbonate as a yellow oil.

The propylene trithiocarbonate (130 g., 0.87 mole) was slowly added to a solution of potassium hydroxide (210 g., 3.7 mole) in 800 ml. of methanol. The reaction mixture, which became warm during the addition, was allowed to stand at 25° overnight and was then slowly added to ice-cold 6N sulphuric acid covered with a layer of ether. After complete addition, the ether layer was separated, dried over magnesium sulphate and then fractionally distilled under a nitrogen atmosphere to give

52.5 g. (49%) of 1,2-dimercaptopropane boiling at 67°/40 mm. Lit. b.p. 72-74°/55mm (66).

3-Mercapto-1-propanol was prepared by the method described in the literature by Rojan and Lemme (67).

A solution of sodium hydroxide (50 g., 1.25 mole) in 50 ml. of water was added to 300 ml. of methanol. The resulting solution was saturated with hydrogen sulphide at 0° and then 3-chloro-1-propanol (94.5 g., 1.0 mole) was added and the reaction mixture allowed to stand at 45° for 1 hour under an atmosphere of nitrogen, then cooled and acidified by the addition of acetic acid. The resulting solution was concentrated by distillation of the solvent and then poured into cold water. The product was extracted with ether, the etheral extract dried over magnesium sulphate and then fractionated to give 38 g. (41%) of material boiling at 75°/10mm. Lit. b.p. 85-90°/15mm. (67).

2-Phenyl-1,3-oxathiane was prepared by the method of Djerassi and Gorman (31).

Benzaldehyde (60 g., 0.57 mole) and 3-mercapto-1-propanol (46 g., 0.50 mole)were dissolved in 200 ml. of toluene containing p-toluenesulphonic acid (0.5 g.). The resulting solution was boiled under reflux with a condenser equipped with a Dean and Stark trap (32) until the theorectical amount of water (9 ml.) was collected. This usually required two hours. The solution was then cooled, extracted with aqueous sodium carbonate

solution and then with water and dried over anhydrous magnesium sulphate. Removal of the solvent by distillation afforded the product as a straw-coloured oil which was purified by fractional distillation under reduced pressure, to give 79.6 g. (88.5%) of material boiling at 116°/3mm. Lit. b.p., 166°/1.2mm. (21). A sample prepared for analysis boiled at 92°/1.0mm.

Calc. for $C_{10}H_{12}OS$: C. 66.67 : H. 6.67 : S.17.78.
Found : C. 66.53 : H. 6.83 : S. 17.56.

The following compounds were prepared by procedures similar to that described for 2-phenyl-1,3-oxathiane.

2-Phenyl-1,3-oxathiolane was prepared in 81% yield from benzaldehyde and 2-mercaptoethanol. Purification of the product by fractional distillation under reduced pressure afforded a material boiling at 92°/6 mm. Lit. b.p. 86-87°/5 mm. (68).

2,2-Diphenyl-1,3-oxathiolane was prepared in 25% yield from benzophenone and 2-mercaptoethanol. The product after crystallisation from methanol, melted at 51-52°. Lit. m.p. 52° (7).

2-Phenyl-1,3-dithiolane was prepared in 77% yield from benzaldehyde and 1,2-dimercaptoethane. The material was purified by distillation under reduced pressure b.p. 119°/2 mm. m.p. 25°. Lit. m.p. 29° (69).

4-Methyl-2-phenyl-1,3-dithiolane was prepared in 81% yield from benzaldehyde and propan-1,2-dithiol. Purification

by distillation under reduced pressure afforded a material of b.p. 165°/24 mm. Lit. mp. 123°/3mm. (36).

2-n-Propyl-1,3-oxathiolane was prepared according to a modification of the general procedure recommended in the literature by Djerassi and Gorman (31), by condensation of n-butyraldehyde with 2-mercaptoethanol.

n-Butyraldehyde (40 g., 0.56 mole) and 2-mercaptoethanol (36 g., 0.46 mole) were dissolved in 200 ml. of dry benzene. To this was added 0.3 g. of p-toluenesulphonic acid and 20 g. of anhydrous magnesium sulphate. The resulting mixture, which became warm upon the addition of these reagents, was allowed to stand for 20 hours and then poured into aqueous sodium carbonate solution. The organic layer was separated, dried over anhydrous magnesium sulphate and then fractionally distilled. There was obtained 50 g. (82%) of 2-n-propyl-1,3-oxathiolane boiling at 84°/34 mm. n_D^{25}. 1.4709.

Calc. for $C_6H_{12}OS$: C. 54.54, H. 9.09 : S. 24.24.
Found : C. 54.63 : H. 9.17 : S. 24.01.

2,4-Dimethyl-1,3-dithiolane was prepared according to the above procedure by condensation of acetaldehyde with 1,2-dimercaptopropane.

Yield 77%., B.p. 81°/25 mm. n_D^{25}. 1.5434
Calc. for $C_5H_{10}S_2$: C. 44.78 : H. 7.46 : S. 47.76.
Found : C. 44.55 : H. 7.47 : S. 47.91.

2-n-Propyl-1,3-dioxolane was prepared according to the aforementioned procedure by condensation of n-butyraldehyde

with ethylene glycol.

Yield, 65%. B.p. 131-2°/100 mm. Lit. b.p., 132-3° (70).

2,2-Dimethyl-1,3-oxathiolane was prepared by a further modification of the general procedure as recommended in the literature (31), by condensation of acetone with 2-mercaptoethanol.

2-Mercaptoethanol (39 g., 0.5 mole) was added to 200 ml. of dry acetone containing 1 g. of p-toluenesulphonic acid and 20 g. of anhydrous magnesium sulphate. The resulting mixture was allowed to stand for 24 hours at room temperature and then filtered free of inorganic material. Fractional distillation of the filtrate afforded 48 g. (81%) of the required material boiling at 132°/100 mm. Lit. b.p., 70°/65 mm. (31).

2,2-Dimethyl-1,3-dithiolane was prepared according to the above procedure by condensation of acetone with 1,2-dimercaptoethane.

Yield, 95%. B.p. 65°/11 mm. Lit. b.p., 171° (71).

4-Hydroxymethyl-2-phenyl-1,3-dithiolane was prepared by the method advocated by Roberts and Cheng (36).

2,3-Dimercapto-1-propanol (24.8 g., 0.2 mole) was added to a solution of benzaldehyde (22.0 g., 0.21 mole) in 150 ml. of methylene chloride containing 0.2 g. of p-toluenesulphonic acid and 20 g. of anhydrous magnesium sulphate. The reaction mixture which became warm on addition of the thiol was allowed to stand for

three hours at room temperature and then poured into cold water.

The organic layer was separated, washed twice with saturated sodium bisulphite solution, then once with saturated sodium carbonate solution and finally with water and then dried over anhydrous magnesium sulphate. Removal of the solvent by distillation yielded the product as a pale yellow oil which solidified upon cooling. The resulting solid was crystallised from benzene-skellysolve to give 19.0 g., (45%) of material melting at 68-70°. Lit. m.p., 68-71° (36).

An N.M.R. spectrum of this material showed it to be approximately a 1:1 mixture of the two possible geometrical isomers.

4-(3',5'-Dinitrobenzoxymethyl)-2-phenyl-1,3-dithiolane was prepared by the method of Roberts and Cheng (36).

A solution of the isomeric mixture of 4-hydroxymethyl-2-phenyl-1,3-dithiolane (42.4g., 0.2 mole) in a mixture of benzene (500 ml.) and pyridine (50 ml.) was treated with a benzene solution of 3,5-dinitrobenzoyl chloride (50 g., 0.22 mole). The resulting mixture was allowed to stand at 25° for 20 hours and then poured into cold water. At this stage 500 ml. of ethyl acetate was added to prevent precipitation of the product. The organic layer was isolated, washed several times with sodium bicarbonate solution, then with water and finally dried over anhydrous magnesium sulphate. Removal of the solvent

afforded a yellow crystalline solid which was freed from extraneous material by digesting with 1 l. of a 10% solution of acetone in water (warm) for 15 minutes. The product was then collected and air-dried. Yield, 70 g. (86%), m.p. 86-91°. Lit. m.p. 91-94° (36).

This material consisted of a mixture of the two geometrical isomers, which were separated by the following procedure.

The mixture of isomers (40 g.) was dissolved in 400 ml. of boiling benzene. The benzene solution was cooled and the resulting precipitate collected. Recrystallisation of this precipitate from benzene afforded 15.0 g. (37.5%) of the high-melting isomer of 4-(3′,5′-dinitrobenzoxymethyl)-2-phenyl-1,3-dithiolane which melted at 117-8°, Lit. m.p. 112-3° (36).

Concentration of the filtrate, from the initial crystallisation, by evaporation gave the impure low-melting isomer. This was collected, washed with ether (100 ml.) and then dissolved in a minimum volume of boiling benzene. The solid which separated on cooling the solution was removed by filtration and rejected. The resulting filtrate was concentrated to give a solid. Two crystallisations from ethanol yielded the pure low-melting isomer of 4-(3′,5′-dinitrobenzoxy)-2-phenyl-1,3-dithiolane which melted at 99-100°, Lit. m.p. 100-101° (36).

4-Hydroxymethyl-2-phenyl-1,3-dithiolane (high-melting isomer) was obtained by hydrolysis of the high-melting

3,5-dinitrobenzoate ester. The method described in the literature (36) proved unsatisfactory but the following procedure, a modification of Roberts and Chengs' method, gave good results.

The high-melting isomer of the 3,5-dinitrobenzoate ester of 4-hydroxymethyl-2-phenyl-1,3-dithiolane (4.6 g.) was added to a solution of potassium hydroxide (6 g.) in a mixture of 25 ml. of ethanol and 25 ml. water. The mixture was stirred and refluxed for 30 minutes and then poured into cold water whereupon the product separated as a crystalline solid. The solid was collected and purified by chromatography on an alumina column with ether as eluant. Subsequent crystallisation from benzene-skellysolve afforded the pure product, m.p. 89-90°. Lit. m.p. 88.5-90° (36).

Low-melting isomer of 4-hydroxymethyl-2-phenyl-1,3-dithiolane

This compound was obtained by the same procedure as for the high-melting isomer. Commencing with 6.2 g. of the low-melting 3,5-dinitrobenzoate ester there was obtained 2.2 g. (68%) of the low melting alcohol m.p. 87-8°. Lit. m.p., 87.5-88° (36).

High-melting isomer of 4-chloromethyl-2-phenyl-1,3-dithiolane (Assumed structure)

A solution of the high-melting isomer of 4-hydroxymethyl-2-phenyl-1,3-dithiolane (1.8 g. 0.0085 mole) in 30 ml. of di*iso*propyl ether was treated with one

drop of pyridine and then with thionyl chloride (1.0 g., 0.0085 mole). The resulting mixture was refluxed for two hours then cooled and poured into cold sodium carbonate solution. The organic material was extracted with ether, the ether extract washed twice with sodium bicarbonate solution and dried over anhydrous sodium carbonate. Removal of the solvent afforded a pale yellow solid which was purified by chromotography on alumina using Skellysolve B as eluant. Crystallisation from skellysolve gave an analytical sample of m.p., 68-69°. Yield; 0.9 g. (46%).

Calc. for $C_{10}H_{11}ClS_2$: C,52.06 : H,4.77 : Cl,15.40 : S,27.77.
Found : C,51.74 : H,4.52 : Cl,15.17 : S,28.01.

The *low-melting isomer of 4-chloromethyl-2-phenyl-1,3-dithiolane** was prepared in 58% yield in a manner identical to that used to prepare the high melting isomer. An analytical sample melted at 60-62°.

Calc. for $C_{10}H_{11}ClS_2$: C,52.06 : H,4.77 : Cl,15.40 : S,27.77.
Found : C,51.80 : H,4.64 : Cl,15.61 : S,27.61.

An authentic sample of a mixture of the above isomers was prepared in 65% yield from the unresolved mixture of the 4-hydroxymethyl-2-phenyl-1,3-dithiolanes. An analytical sample of this mixture melted over the broad range 57-62°.

Calc. for $C_{10}H_{11}ClS_2$: C,52.06 : H,4.77 : Cl,15.40 : S,27.77.
Found : C,51.83 : H,4.44 : Cl,15.59 : S,27.90.

* Assumed structure of product.

II Preparation of Authentic Samples of the Reduction Products of the 1,3-Oxathiolanes and 1,3-Oxathianes.

Benzyl γ-hydroxy-n-propyl sulphide was prepared by the method of Rothstein (72).

3-Mercapto-1-propanol (9.2 g., 0.1 mole) was added to a solution of sodium methoxide (0.1 mole) in 100 ml. of methanol. Benzyl chloride (14.0 g., 0.1 mole) was added dropwise and the resulting mixture was refluxed for one hour. The mixture was cooled and poured into water from which the product was extracted with ether. The etheral extract was dried over anhydrous magnesium sulphate, the solvent removed by distillation, and the residual oil purified by fractional distillation under reduced pressure to give 13.5 g. (74%) of the required material which boiled at 129°/1.6 mm. Lit. b.p. 185°/19 mm. (72).

Benzyl β-hydroxyethyl sulphide was prepared in 68% yield, by an identical procedure to that described above, commencing with benzyl chloride and 2-mercaptoethanol. b.p., 115°/2 mm. Lit. b.p. 169°/18 mm. (73).

β-Hydroxyethyl isopropyl sulphide was prepared in 72% yield by the reaction of 2-mercaptopropane with 2-chloroethanol in ethanol in the presence of potassium hydroxide using the method previously described. B.p. 88°/19 mm. Lit. b.p. 90°/21 mm. (21).

n-Butyl β-hydroxyethyl sulphide was prepared by the reaction of n-butyl bromide with 2-mercaptoethanol in methanol in the presence of sodium hydroxide. Yield 91%.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

B.p., 68°/3 mm. Lit. b.p. 74°/4 mm. (73).

2-n-Butoxyethanol was obtained as a commercial sample.

III The Reduction of 1,3-Oxathiolanes and 1,3-Oxathianes by Lithium Aluminum Hydride and Aluminum Chloride

The reduction of 2-phenyl-1,3-oxathiane is given as a typical reduction procedure.

To a stirred mixture of 2-phenyl-1,3-oxathiane (12.0 g., 0.067 mole) and lithium aluminum hydride (2.7 g., 0.067 mole) in 150 ml. of ether at room temperature was added, over a period of five minutes, a solution of anhydrous aluminum chloride (8.9 g., 0.067 mole) in 100 ml. of ether. The exothermic reaction which occurred during the addition required the slow admixture of the aluminum chloride. The resulting mixture, first stirred for 2 hours, was then cautiously diluted with cold water to destroy the aluminum chloride complexes and the excess hydride. The inorganic material was removed by filtration and the etheral filtrate then dried over magnesium sulphate. Removal of the ether and distillation of the resulting oil under reduced pressure gave a yield of 6.5 g. (54%) of material boiling at 126°/1.6 mm. The infra-red spectrum of this material was identical with that of a sample of benzyl γ-hydroxy-n-propyl sulphide (Lit. b.p. 185°/19 mm. (72)) whose preparation is described on Page 118.

The results of the study of the reduction of hemithioacetals and ketals are tabulated in

Table I, Page 20. The procedure for the reduction was identical to that described here in all cases where lithium aluminum hydride and aluminum chloride were used as the reducing agent.

IV The Attempted Reduction of 1,3-Dithiolanes

The procedure used in all of the attempted reductions of the 1,3-dithiolanes by a combination of lithium aluminum hydride and aluminum chloride is exemplified here by a description of the attempted reduction of 2-phenyl-1,3-dithiolane.

To a stirred mixture of 2-phenyl-1,3-dithiolane (18.3 g., 0.1 mole) and lithium aluminum hydride (1.9 g., 0.05 mole) in 120 ml. of ether at room temperature was added a solution of aluminum chloride (13.4 g., 0.1 mole) in 60 ml. of ether over a period of five minutes. The resulting mixture was then stirred for 2 hours. Following careful treatment of the mixture with water to decompose any aluminum complexes and excess hydride, the precipitated inorganic material was removed by filtration. The etheral filtrate was dried over anhydrous magnesium sulphate, the ether then removed by distillation and the residual oil distilled to yield 17.5 g. (96%) of material whose infrared spectrum was identical to that of the original 2-phenyl-1,3-dithiolane.

A second attempt at reduction using the same conditions but with twice the amount of hydride and with the reaction time increased to 48 hours, also

gave a 96% recovery of starting material. No evidence of reduction was found.

The results of attempted reductions of other 1,3-dithiolanes by this procedure are to be found in Table II, Page 21.

V Comparison of the Rates of Reduction of 2-n-Propyl-1,3-dioxolane and 2-n-Propyl-1,3-oxathiolane

The following specific procedure was used for four separate reductions of 2-n-propyl-1,3-oxathiolane and for one of 2-n-propyl-1,3-dioxolane. These differed only in the length of time that the reaction was allowed to proceed after admixture of all reagents. Times of 20, 40, 60 and 210 minutes were chosen for the oxathiolane reductions while a 20 minute reduction time sufficed for the dioxolane.

To a stirred mixture of the acetal (0.05 mole) and lithium aluminum hydride (0.05 mole) in 70 ml. of ether was added, at room temperature over a period of one minute, a solution of aluminum chloride (0.05 mole) in 30 ml. of ether. The mixture was then stirred and then diluted carefully with cold water. After removal of the inorganic material by filtration, the ether extract was dried over magnesium sulphate. The residual oil obtained on removal of the ether was analysed by g.l.c. The results are shown in Table IV, Page 28.

VI Reduction of 1,3-Oxathiolanes with a Combination of Lithium Aluminum Hydride and Boron Trifluoride

Method a. A mixture of 2,2-dimethyl-1,3-oxathiolane (5.9 g., 0.05 mole) and finely divided lithium aluminum hydride (1.9 g., 0.05 mole) in 75 ml. of anhydrous ether was stirred while boron trifluoride etherate (7.2 g., 0.05 mole) was added dropwise over a period of 15 minutes. After the addition, the solution was stirred for 3 hours at room temperature. After cautious addition of water, followed by removal of inorganic precipitate, the ether layer was separated and dried over magnesium sulphate. Removal of the ether left an oil (5.5 g., 94%) which g.l.c. analysis showed to consist of 39% of β-hydroxyethyl *iso*propyl sulphide and 61% of unchanged starting material.

Method b. In this experiment, a mixture of 2,2-dimethyl-1,3-oxathiolane (5.9 g., 0.05 mole) and boron trifluoride etherate (7.2 g., 0.05 mole) in 75 ml. of ether was stirred whilst powdered lithium aluminum hydride (1.9 g., 0.05 mole) was added in small batches. The remainder of the procedure followed that for method (a). Total yield of material was 73% of which 50% was β-hydroxyethyl *iso*propyl sulphide and 50% the unchanged oxathiolane. The low yield was due to the occurrence of resinous material.

Method c. The same procedure as in method (b) was followed except that the hydride was added in the form of lumps. The overall total yield was 75%, 56% of which was β-hydroxyethyl *iso*propyl sulphide and the remainder (44%) was

unreacted starting material. Here again the formation of resinous material reduced the yield.

Method d. 2,2-Dimethyl-1,3-oxathiolane (5.9 g., 0.05 mole) in 50 ml. of ether was added to a mixture of lithium aluminum hydride (1.9 g., 0.05 mole) and boron trifluoride etherate (7.2 g., 0.05 mole) in 50 ml. of ether. After addition the reaction mixture was stirred for 3 hours. The remainder of the procedure followed that for method (a). Total yield of material was 90% of which less than 1% was reduced material.

During the initial additon of the boron trifluoride etherate to the etheral suspension of lithium aluminum hydride there occurred a vigorous evolution of a gas, presumably diborane.

VII Equilibration of cis- and trans-4-Chloromethyl-2-phenyl-1,3-dithiolane

In diethyl ether as solvent. A solution of 230 mg. of the isomer melting at 68-69° in 20 ml. of ether was treated with 135 mg. of anhydrous aluminum chloride in 10 ml. of ether. The reaction mixture was allowed to stand at room temperature for 20 hours and then poured into aqueous sodium bicarbonate. The ether layer was separated and dried. Evaporation of the solvent afforded 100 mg. of product melting sharply at 67-68°. N.m.r. analyses indicated that no equilibration had occurred since only one sharp singlet occurred at τ = 4.43 characteristic of the C_2 proton of the high-melting isomer.

When boron trifluoride etherate was used as the Lewis acid, the same results were obtained.

In methylene chloride as solvent. A quantity (290 mg.) of the isomer melting at 68-69° was dissolved in methylene chloride previously dried for 48 hours over $CaCl_2$. Anhydrous boron trifluoride was bubbled into the solution for several minutes and the resulting solution allowed to stand for 90 minutes. The solution was then poured into aqueous sodium bicarbonate. The organic layer was separated, washed with aqueous bicarbonate, then with water and finally dried (Na_2CO_3). Evaporation of the solvent gave 225 mg. of material melting at 51-54°. An n.m.r. spectrum (CS_2) of this product indicated a mixture of cis- and trans-4-chloromethyl-2-phenyl-1,3-dithiolane in which the high-melting isomer predominated slightly over the low-melting isomer as determined by the integrated areas and by visual inspection of the two singlets at $\tau = 4.43$ and 4.48.

The same reaction was carried out using $AlCl_3$ as the catalyst rather than BF_3, and allowing the reaction mixture to stand for 20 hours. When the mixture was worked up as before, a resinous material was obtained. An n.m.r. spectrum of this substance indicated extensive decomposition and nothing definite concerning isomerisation.

A repetition of the reaction with $AlCl_3$ as catalyst, but for a period of 4 hours, gave a

resinous oily product whose n.m.r. spectrum showed a somewhat broader and poorly resolved signal at 4.46 , indicating that isomerisation had occurred along with decomposition.

PART B The Reduction of 1,3-Dioxolanes and 1,3-Dioxanes

I. The Preparation of Precursors

a) Epoxides.

1,2-Epoxyethane, 1,2-epoxypropane, 1,2-epoxyethylbenzene and 1,2-epoxy-3-isopropoxypropane were obtained as commercial products from Eastman Kodak Co. Inc., Rochester, New York, U.S.A. 1-Chloro-2,3-epoxypropane was obtained commercially from Matheson, Coleman and Bell, Inc., Norwood, Cincinnati, Ohio, U.S.A.

b) Acids.

Methoxyacetic acid and Ethoxyacetic acid were obtained as commercial products from Eastman Kodak Co. Inc.,

Chloroacetic acid and α-chloropropionic acid were obtained commercially from Fisher Scientific Co., Fair Lawn, New Jersey, U.S.A.

α-Methoxyisobutyric acid was prepared by the procedure described in the literature by Weizman et al. (74) as follows.

Potassium hydroxide (44.8 g., 0.8 mole) was dissolved in a mixture of methanol (100 ml.) and water (25 ml.). The resulting solution was stirred and cooled whilst a solution of 2-methyl-1,1,1-trichloro-2-propanol (35.5 g., 0.2 mole, obtained from Eastman Kodak,

Co., Inc.) in 70 ml. of methanol was slowly added. The resulting mixture was stirred for 1 hour at 25° and then refluxed for 2 hours. The inorganic salt was removed by filtration and the filtrate concentrated by removal of the major portion of the solvent by distillation. The residual oil was acidified with 6N sulphuric acid and the product was isolated by ether extraction. The ethereal extract was dried over magnesium sulphate, the solvent removed by distillation, and the residual oil purified by distillation under reduced pressure to give 14.2 g. (60%) of product which boiled at 84-5°/7 mm. Lit. b.p. 98-99°/20 mm. (74).

The following α-alkoxy*iso*butyric acids were prepared by this method.

α-Ethoxy*iso*butyric acid was prepared in 36% yield from ethanol and 2-methyl-1,1,1-trichloro-2-propanol. B.p. 85-6°/7 mm. Lit. b.p. 97°/19 mm. (74).

α-*iso*Propoxy*iso*butyric acid was prepared in 25% yield from *iso*propanol and 2-methyl-1,1,1-trichloro-2-propanol. B.p. 94-5°/7 mm. Lit. b.p. 106°/15 mm (74).

α-Benzyloxy*iso*butyric acid was prepared in 34% yield from benzyl alcohol and 2-methyl-1,1,1-trichloro-2-propanol. However the procedure was modified somewhat in that the reaction mixture was heated at 100° for 2 hours rather than refluxed for the same length of time. B.p. 139°/3 mm. n_D^{25} 1.5048.

Calc. for $C_{11}H_{14}O_3$: C, 68.04 : H, 7.22.

Found : C, 68.36 : H, 7.02.

c) Esters:- Benzylchloroacetate, isopropenylacetate, ethyl chloroacetate, ethyl 2-bromopropionate and ethyl β-ethoxypropionate were obtained commercially from Eastman Kodak Co. Inc., Rochester New York, U.S.A.

Methyl α-chloropropionate was prepared by acid-catalysed esterification of α-chloropropionic acid as follows.

A mixture of α-chloropropionic acid (108.5 g., 1.0 mole), methanol (400 ml.) and concentrated sulphuric acid (20 ml.) was refluxed for 3 hours, then cooled and poured into an aqueous solution of sodium carbonate. The organic layer was separated, washed with sodium carbonate solution, dried over anhydrous sodium carbonate, and then distilled to give 41 g. (33%) of material boiling at 127-9°/700 mm. Lit. b.p., 127-130° (75).

The following esters were prepared from the corresponding alcohol and acid by similar procedure to that described above:-

n-Propyl α-chloropropionate was prepared in 70% yield from 1-propanol and α-chloropropionic acid. B.p. 68°/23 mm. Lit. b.p. 57°/12 mm. (76).

iso-Propyl chloroacetate was prepared in 60% yield from 2-propanol and chloroacetic acid. B.p. 66°/25 mm. Lit. b.p. 150° (77).

Ethyl methoxyacetate was prepared in 59% yield from ethanol and methoxyacetic acid. B.p. 138-9°/700 mm. Lit. b.p. 144°/748 mm. (78).

Ethyl ethoxyacetate was prepared in 62% yield from ethanol and ethoxyacetic acid. B.p. 152-3°. Lit. b.p.154° (79).

Methyl α-methoxypropionate was prepared by the following procedure as advocated by Nieman *et al.* (75).

Methyl α-chloropropionate (24.5 g., 0.2 mole) was added dropwise to a stirred solution of sodium methoxide (from 5.0 g., 0.22 mole of sodium) in 50 ml. of methanol. The resulting mixture was refluxed for 3 hours, cooled and filtered free from sodium chloride. The filtrate was concentrated by removal of the major portion of the solvent by distillation and then poured into cold water. The product was extracted with ether, the etheral extract dried over anhydrous magnesium sulphate, and then fractionally distilled to give 6.7 g. (28%) of material boiling at 127-9°/700 mm. Lit. b.p., 127-9° (75).

The following esters were prepared in a similar manner.

Ethyl α-ethoxypropionate was prepared in 64% yield from sodium ethoxide and ethyl α-bromopropionate in ethanol as solvent. B.p. 70°/30 mm. Lit. b.p. 68°/27 mm. (80).

n-Propyl α-*n*-propoxypropionate was prepared in 79% yield from sodium *n*-propoxide and *n*-propyl α-chloropropionate in 1-propanol as solvent. B.p. 85°/16 mm. Lit. b.p. 187-8° (81).

iso-Propyl α-*iso*propoxypropionate was prepared in 54% yield from sodium *iso*propoxide and *iso*propyl α-chloropropionate in 2-propanol as solvent. B.p. 78°/23 mm.

Calc. for $C_9H_{18}O_3$: C, 62.07 : H, 10.34.
Found : C, 61.93 : H, 10.15.

iso-Propyl isopropoxyacetate was prepared in 75% yield commencing from sodium isopropoxide and isopropyl chloroacetate in 2-propanol. B.p. 65°/8 mm.

Calc. for $C_8H_{16}O_3$: C, 60.00 : H, 10.00.
found : C, 60.13 : H, 10.25.

Ethyl benzyloxyacetate was prepared in 23% yield from ethyl chloroacetate and sodium benzyloxide in benzyl alcohol as solvent. B.p. 118-20°/3 mm. Lit. b.p. 100-102°/1mm. (82).

Ethyl α-hydroxyisobutyrate was conveniently prepared by the following procedure, as advocated in the literature by Hepworth (83).

A suspension of magnesium turnings (10 g.) in anhydrous ether (400 ml.) was stirred and cooled in ice whilst methyl iodide (10 g.) was added. After the reaction had commenced, a mixture of methyl iodide (170 g., 1.2 mole) and diethyl oxalate (73 g., 0.5 mole) was added at such a rate that the reaction proceeded slowly (time for addition, ca. 2 hours.). Magnesium turnings (20 g.)were added in portions from time to time so as to keep the metal always in excess. When the reaction mixture had stood at 25° for 2 hours after complete addition of the reagents, ice was added followed by 6M sulphuric acid until all of the magnesium hydroxide had dissolved. The etheral layer was separated, washed with an aqueous

solution of sodium carbonate, then water and finally dried over anhydrous sodium carbonate. Removal of the ether by distillation afforded an oil which was distilled under reduced pressure to give 24.5 g. (37%) of material boiling at 58°/25 mm. Lit. b.p., 150-151°. (83).

"Mixed" diesters of *iso*Propoxymalonic acid was prepared by the following procedure described in the literature by Ames and Bowman (84).

*Iso*propyl *iso*propoxyacetate (55 g. 0.34 mole) was added to a suspension of sodium methoxide (18.5 g., 0.34 mole) in anhydrous diethylcarbonate (350 ml.) The mixture was slowly distilled through a 30 cm. Vigreux column until no more ethanol distilled over. The sodio derivative of *iso*propoxymalonic ester which separated as a white solid when the reaction mixture was cooled, was collected, washed with dry benzene and then decomposed by suspending it in benzene and shaking with dilute sulphuric acid. The organic layer was separated, washed with water, dried over anhydrous magnesium sulphate and then distilled to afford 30 g. of material boiling at 89°/1.5 mm.

The structure of the product was confirmed by converting a small quantity of the mixed ester to *iso*propoxymalondiamide by shaking it with concentrated ammonium hydroxide. The diamide separated as a white crystalline solid which was collected and purified by crystallisation from aqueous acetone. m.p. 220-221°.

Calc. for $C_6H_{12}N_2O_3$: C,45.00 : H,7.50 : N,17.50.
Found : C,44.86 : H,7.42 : N,17.37.

d. Diols

Ethylene glycol, 1,3-propanediol, glycerol, 1,2-propanediol, 3-chloro-1,2-propanediol, 1,3-butanediol and 1-phenyl-1,2-ethanediol were obtained commercially from Eastman Kodak Co. Inc.

2-Methyl-1,2-propanediol was prepared by standard laboratory procedures entailing the reduction of ethyl α-hydroxyisobutyrate by lithium aluminum hydride as illustrated.

A solution of ethyl α-hydroxyisobutyrate (52.5 g., 0.4 mole) in 100 ml. of ether was added dropwise to a stirred suspension of lithium aluminum hydride (15.2 g., 0.4 mole) in 500 ml. of ether. After complete addition the reaction mixture was allowed to stand for 2 hours and then water was cautiously added to decompose any excess hydride and aluminum complexes. The inorganic solid was then removed by filtration and the filtrate dried over anhydrous magnesium sulphate. Removal of the ether by distillation afforded the required product as an oil which was purified by distillation under reduced pressure to give 25.2 g. (70%) of material boiling at 55°/3 mm. Lit. b.p., 80°/12 mm. (85).

1-isoPropoxy-2,3-propanediol was prepared by acid hydrolysis of the corresponding epoxide after the method advocated in the literature by Lucas et al. (86).

1,2-Epoxy-3-isopropoxypropane (25 g., 0.22 mole) was added to a stirred mixture of water (40 ml.) and concentrated sulphuric acid (2 ml.) at 60°. During

the addition the temperature of the reaction mixture rose to 95° and was kept at this temperature for 30 minutes after complete addition of reagents and then cooled. Solid sodium carbonate was added to completely neutralise the acid and the product was then extracted with ether and dried over sodium carbonate. Removal of the ether by distillation afforded an oil which was distilled under reduced pressure to give 21.4 g. (74%) of material boiling at 94°/ 3.5 mm. Lit. b.p., 187°-90° (87).

e. Acetals and ketals

1-Chloro-2,2-diethoxyethane, 1,3,3-Trimethoxy-1-propene 1-chloro-2,2-dimethoxyethane and diethoxymethane were obtained as commercial products from Eastman Kodak Co. Inc.

2,2-Dimethoxypropane was prepared by the method described in the literature by Croxall *et al.* (47).

Isopropenylacetate (50 g., 0.5 mole) was added to methanol (32 g., 1.0 mole) containing 0.5 g. of mercuric oxide and 0.5 ml. of boron trifluoride etherate. The temperature of the reaction mixture was maintained below 55° during the addition by immersion of the reaction vessel in cold water. The reaction mixture was stirred for one hour and then poured into a saturated aqueous solution of sodium carbonate. The product was extracted with ether, dried over anhydrous sodium carbonate and then fractionally distilled to yield 19.1 g. (41%) of product boiling at 79-80°/ 700 mm. Lit. b.p., 83° (88).

1,1-Dichloro-2,2-diethoxyethane was prepared following the procedure described by Fritsch (89).

Chlorine gas was bubbled through ethanol (100 ml.) at 25° for six hours, after which time the lower layer of the reaction mixture was isolated and mixed with 100 ml. of ethanol. The resulting solution was treated with sodium carbonate (solid) and then poured into aqueous sodium carbonate solution. The oil that was precipitated was isolated with ether and the ether extract dried over anhydrous sodium carbonate. Removal of the ether by distillation afforded an oil which was purified by fractionnal distillation under reduced pressure to give 15 g. of material which boiled at 74-5°/20 mm. Lit. b.p. 66-71°/12 mm. (90).

II. The Preparation of 1,3-Dioxolanes and 1,3-Dioxanes

2-Phenyl-1,3-dioxane was prepared by the procedure described in the literature by Salmi (91).

Benzaldehyde (60 g., 0.57 mole), 1,3-propanediol (38 g., 0.5 mole), *p*-toluenesulphonic acid (1 g.) and toluene (150 ml.) were heated under a reflux condenser containing a Dean and Stark water-separator (32) until the requisite amount of water (9 ml.) had been taken off. The reaction mixture was then cooled and poured into saturated sodium bicarbonate solution. The organic layer was separated, washed with water and dried over anhydrous sodium carbonate. Fractional distillation of the organic layer, under reduced pressure, afforded 55 g. (67%) of material

2 mm ?

which boiled at 95-6°/12 mm. This oil solidified on cooling and after crystallisation from skellysolve melted at 45-6° Lit. m.p., 49-51° (92).

2-Phenyl-1,3-dioxolane was prepared in 57% yield by the method described above, commencing with benzaldehyde and 1,2-ethanediol. B.p., 116°/20 mm. Lit. b.p. 101°/10 mm. (93).

4,4-Dimethyl-2-phenyl-1,3-dioxolane was prepared from benzaldehyde and 2-methyl-1,2-propanediol in 70% yield by the above procedure. B.p. 85°/5 mm. n_D^{25}. 1.5015.

Calc. for $C_{11}H_{14}O_2$: C, 74.16 : H, 7.87
Found : C, 74.26 : H, 8.06.

The following formals were prepared by a modification of the procedure described by Vogel (94), and illustrated here by a description of the preparation of 4-methyl-1,3-dioxolane.

4-Methyl-1,3-dioxolane A mixture of paraformaldehyde (33 g., 1.1 mole), 1,2-propanediol (76 g., 1.0 mole) anhydrous magnesium sulphate (30 g.) and 2 ml. of concentrated hydrochloric acid was refluxed for five hours. The reaction was cooled and filtered. The filtrate was dried over anhydrous magnesium sulphate and then fractionally distilled to give 55 g. (65.5%) of material boiling at 82-3°/700 mm. Lit. b.p., 88-9°/755 mm. (95).

4-Chloromethyl-1,3-dioxolane was prepared in 82% yield from paraformaldehyde and 3-chloro-1,2-propanediol. B.p.,

76°/54 mm. Lit. b.p., 126°/750 mm. (96).

4-Phenyl-1,3-dioxolane was prepared in 75% yield from paraformaldehyde and 1-phenyl-1,2-ethanediol. B.p., 66°/1.4 mm. Lit. b.p., 101°/12 mm. (97).

4,4-Dimethyl-1,3-dioxolane was prepared in 51.5% yield from paraformaldehyde and 2-methyl-1,2-propanediol. However in this case the reaction time was 20 minutes. B.p., 100-102°/700 mm. n_D^{25}. 1.4004.

Calc. for $C_5H_{10}O_2$: C, 58.82 : H, 9.80.
Found : C, 58.46 : H, 10.06.

1,3-Dioxolane was prepared by a modification of the method advocated by Vogel (94).

A mixture of 1,2-ethanediol (32 g., 0.5 mole), paraformaldehyde (20g., 0.67 mole), anhydrous magnesium sulphate (20 g.) and 2 ml. of concentrated hydrochloric acid was heated at such a rate that the product was taken off through a 4" Vigreux column as it was formed. The product was collected, dried over anhydrous sodium carbonate, filtered and refractionated to give the required material of boiling point 71-3°/700 mm. Lit. b.p., 74-5° (98).

1,3-Dioxane was prepared in 50% yield by the same method as used for the preparation of 1,3-dioxolane, commencing with paraformaldehyde and 1,3-propanediol. B.p. 101°/700 mm. Lit. b.p., 105° (95).

The following ketals were prepared in accordance with the procedure described in the literature by Fischer and Pfahler (45) and which is illustrated here by a description of the preparation of 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane.

2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane.

A mixture of glycerol (100 g., 1.09 mole), anhydrous magnesium sulphate (40 g.,), p-toluenesulphonic acid (1 g.) and acetone (600 ml.) was allowed to stand at 25° for 60 hours and then filtered. The filtrate was concentrated to a small volume, by removal of the solvent by distillation, and poured into a saturated aqueous solution, of sodium carbonate. The product was isolated by ether extraction, the etheral extract dried over anhydrous magnesium sulphate and then distilled to yield 116 g. (80%) of material boiling at 95°/24 mm. Lit. b.p., 82.5°/11 mm. (45).

2,2-Dimethyl-4-phenyl-1,3-dioxolane was prepared in 79% yield by the above procedure, commencing with 1-phenyl-1,2-ethanediol and acetone.
B.p., 73°/2 mm. Lit. b.p., 95-6°/10 mm. (99).

2,2,4-Trimethyl-1,3-dioxolane was prepared from 1,2-propanediol and acetone in 33% yield by the above method.
B.p., 99°/700 mm. Lit. b.p., 98-9° (100).

4-Chloromethyl-2,2-dimethyl-1,3-dioxolane was prepared from 3-chloro-1,2-propanediol and acetone in 78% yield by the above procedure.
B.p., 78°/40 mm. Lit. b.p. 64.5-65°/25 mm. (45).
157/767 mm

2,2-Dimethyl-1,3-dioxolane was prepared from acetone and 1,2-ethanediol in 24% yield by the aforementioned procedure. B.p., 89°/700 mm. Lit. b.p., 92.5°/760 (101).

2,2,4-Trimethyl-1,3-dioxane was prepared from acetone and 1,3-butanediol by the above method. B.p., 125°/700 mm. Lit. b.p., 130-1° (102)

The following dioxolanes were prepared by acetal or ketal exchange reactions by procedures similar to that described in the literature by McElvain and Curry (46).

2,2,4,4-Tetramethyl-1,3-dioxolane

A mixture of 2-methyl-1,2-propanediol (6 g., 0.067 mole), 2,2-dimethoxypropane (7 g., 0.067 mole) and 0.05 g. of *p*-toluenesulphonic acid was heated under a 4" Vigreux column at such a rate that the methanol, formed during the reaction, slowly distilled over. After the theoretical amount of methanol had been taken off, the residual oil was fractionally distilled to give 5.8 (67%) of material boiling at 106°/700 mm. Lit. b.p., 109-110° (103).

4-isoPropoxymethyl-1,3-dioxolane was prepared in 42% yield from 1-*iso*propoxy-2,3-propanediol and 1,1-diethoxymethane. B.p. 70°/20 mm. n_D^{25}. 1.4201.

Calc. for $C_7H_{14}O_3$: C, 57.53 : H : 9.59

Found : C, 57.30 : H : 9.49

2,2-Dimethyl-4-isopropoxymethyl-1,3-dioxolane was prepared in 51% yield from 2,2-dimethoxypropane. B.p., 68°/16 mm. Lit. b.p., 56-7°/10 mm. (99).

2-Chloromethyl-1,3-dioxolane was prepared in 63% yield from 1-chloro-2,2-dimethoxyethane and 1,2-ethanediol. B.p., 154-5°/700 mm. Lit. b.p., 155-159°/740 mm. (46).

2-(Dichloromethyl)-1,3-dioxolane was prepared from 1,2-ethanediol. B.p., 185°/700 mm. Lit. b.p., 185-8° (104)

2,2,4,4,5,5-Hexamethyl-1,3-dioxolane was prepared in 72% yield from 2,2-dimethoxypropane and anhydrous pinacol. B.p., 145-6°/700 mm. Lit b.p., 147.5-148.5°. (105).

2-(Trichloromethyl)-1,3-dioxolane was prepared by the method described by McElvain and Curry (46) as illustrated below.

A mixture of chloral hydrate (42 g., 0.25 mole), 1,2-ethanediol (16 g., 0.25 mole) and concentrated sulphuric acid (30 ml.) was heated at 85° for 4 hours, then cooled and poured onto ice. The organic material was extracted with methylene chloride, the extract dried over anhydrous magnesium sulphate and then the solvent removed by distillation. The residual oil was purified by distillation under reduced pressure to give 13.5 g. (30%) of material boiling at 62°/3 mm. and melting at 38°. Lit. b.p., 85-6°/12 mm. Lit. m.p., 41-2° (46).

2,4-Dimethyl-1,3-dioxolane was prepared by a modification of the procedure described in the literature by Fischer and Pfahler (45).

[illegible]

[illegible]

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[illegible]

[illegible]

[illegible]

[illegible]

Acetaldehyde (100 g., 2.3 mole) was added portionwise to a stirred mixture of 1,2-propanediol, (152 g., 2.0 mole), anhydrous magnesium sulphate (60 g.) and p-toluenesulphonic acid (1 g.). The temperature of the reaction mixture was maintained below 20°, by ice-cooling, during the addition. After complete addition of reagents, the reaction mixture was allowed to stand at 0° for 16 hours, then filtered free from the magnesium sulphate and distilled to give 121 g. (59%) of material boiling at 88-9°. Lit. b.p., 93° (106). G.l.c. analysis of this material showed it to be a mixture of two components, these being the cis and trans isomers of the dioxolane.

Separation of these isomers was effected by fractional distillation through a one metre column packed with stainless steel packing. Several fractional distillations were necessary before each of the isomers was obtained in a sufficient state of purity. The course of the distillation was followed by g.l.c. analysis of the various fractions.

The pure isomers obtained in this manner were finally distilled over sodium hydroxide pellets.

The lower boiling isomer (cis) boiled at 87°/700 mm. Lit. b.p., 89.7° (58).

The higher boiling isomer (trans) boiled at 89-90°/700 mm. Lit. b.p. 93.5°. (58).

2-Ethyl-4-methyl-1,3-dioxolane was prepared by a similar procedure to that described for the preparation of

2,4-dimethyl-1,3-dioxolane.

B.p. 114-7°. Lit. b.p., 113-8° (107).

The two isomers of this compound were separated by fractional distillation through a spinning bond column. Several distillations were necessary before complete separation was achieved. The pure isomers were then stored over sodium hydroxide pellets.

B.p. of trans isomer 117°/700 mm.
B.p. of cis isomer 115°/700 mm.

III The Preparation of Authentic Samples of Reduction Products

3-Methoxy-1-propanol was prepared by the method of Henze and Rogers (108).

Sodium (5.0 g., 0.22 mole) was dissolved in 120 ml. of methanol, the resulting solution was stirred and refluxed whilst 3-chloro-1-propanol (19.0 g., 0.2 mole, obtained from Eastman Kodak Co. Inc.) was added dropwise. The reaction mixture was then refluxed for three hours, cooled and poured into cold water. The product was isolated by ether extraction, the etheral extract dried over anhydrous magnesium sulphate, and then distilled to give 3.8 g. (21%) of material which boiled at 145-6°/700 mm. Lit. b.p., 149°. (109).

3-Benzyloxy-1-propanol was prepared by the procedure described in the literature by Bennett and Hock (110).

Sodium metal (2.7 g., 0.12 mole) was dissolved in 30 ml. of hot 1,3-propanediol. To the resulting solution was added benzyl chloride (15.0 g.,0.12 mole)

and the mixture was then heated at 120° for 2 hours, then cooled and poured into cold water. The product was isolated by ether extraction and the extract dried over anhydrous magnesium sulphate. After removal of the ether by distillation, the residual oil was distilled under reduced pressure to yield 7.2 g. (37%) of material which boiled at 107°/1.5 mm. Lit. b.p., 155°/23 mm. (110).

2-Benzyloxyethanol was prepared in an identical manner to that described immediately above. The yield was 35% commencing from benzyl chloride and 1,2-ethanediol. B.p. 116°/6 mm. Lit. b.p., 138°/15 mm. (111).

4-Methoxy-2-butanol was prepared by the procedure described above. Starting from 1,3-butanediol and methyl iodide. B.p. 85°/62 mm. Lit. b.p., 145° (112).

4-isoPropoxy-2-butanol was prepared by the above method from 1,3-butanediol and 2-bromopropane. B.p. 94°/45 mm. n_D^{25}. 1.451

Calc. for $C_7H_{16}O_2$: C, 63.64 : H, 12.12

Found : C, 63.96 : H, 12.37.

2-Ethoxyethanol was obtained commercially from Eastman Kodak Co. Inc.

The following 1-alkoxy-2-propanols were prepared by the method advocated in the literature by Chitwood and Freure (113). The preparation of 1-*n*-propoxy-2-propanol is described in full detail to illustrate the procedure.

1-n-Propoxy-2-propanol

1,2-Epoxypropane (15.0 g., 0.26 mole) was added dropwise to a solution of sodium n-propoxide (prepared from 2 g. of sodium in 70 ml. of 1-propanol). The resulting solution was allowed to stand at 25° for 16 hours and then poured into cold water. The organic layer was separated, washed with water and then dried over anhydrous magnesium sulphate. After removal of the solvent, by distillation, the remaining oil was distilled under reduced pressure to yield 22.0 g. (72%) of material which boiled at 73°/45 mm. Lit. b.p., 148.5-149°/730 (114).

1-Ethoxy-2-propanol B.p., 130°/700 mm. Lit b.p., 130° (113)

1-Methoxy-2-propanol B.p., 115-6°/700 mm. Lit. b.p., 118-9° (115).

1-isoPropoxy-2-propanol B.p., 68°/40 mm. Lit. b.p., 137-8° (116).

1-Chloro-3-isopropoxy-2-propanol was synthesised by the method described in the literature by Koelsch (117). A general method for the preparation is given here as this and the following compound were prepared on a scale of a few grams solely to obtain a sample for characterisation purposes.

1-Chloro-2,3-epoxypropane (1 mole) was added in a dropwise manner to 2-propanol (10 moles) to which 3 drops of concentrated sulphuric acid had been added. The reaction mixture was maintained at 30° during the addition by cooling in ice-water. The reaction mixture

was allowed to stand for 3 hours after complete addition, then poured into saturated aqueous sodium carbonate solution. The organic layer was separated, dried over anhydrous sodium carbonate and then fractionally distilled under reduced pressure to yield the required product which boiled at 80°/6 mm. Lit. b.p., 87-87.5°/20 mm. (127).

1-Chloro-3-methoxy-2-propanol was prepared by the above method from methanol and 1-chloro-2,3-epoxypropane. B.p., 77°/8 mm. Lit. b.p., 95°/20 mm. (117).

1-isoPropoxy-3-methoxy-2-propanol was prepared according to the above procedure in 65% yield commencing from methanol and 1,2-epoxy-3-isopropoxypropane. B.p., 97°/30 mm. Lit. b.p., 202-3° (118).

1,3-Diisopropoxy-2-propanol was prepared according to the above procedure in 46% yield starting from 2-propanol and 1,2-epoxy-3-isopropoxypropane. B.p., 101°/20 mm. Lit. b.p., 74-5°/2 mm. (108).

2-Ethoxy-1-propanol was prepared by a standard literature procedure (52) involving the lithium aluminum hydride reduction of the corresponding ester or acid as described below.

Ethyl α-ethoxypropionate (28.0 g., 0.19 mole) was added in a dropwise manner to a stirred suspension of lithium aluminum hydride (7.7 g., 0. 2 mole) in 200 ml. of ether. After complete addition of the reagents, the reaction mixture was stirred for one hour and then cold water was cautiously added to decompose any

excess hydride and aluminum salts. After removal of the inorganic solid by filtration, the ether solution was dried over anhydrous magnesium sulphate. Removal of the ether afforded an oil which was purified by distillation to give 16.1 g. (81%) of material which boiled at 143° /700 mm. Lit. b.p., 138° (113).

2-n-Propoxy-1-propanol was prepared in 58% yield in a similar manner to that described above, by lithium aluminum hydride reduction of n-propyl α-n-propoxypropionate. B.p., 154-5° /700 mm. Lit. b.p., 150.5-151° /730 mm. (114).

2-Methoxy-1-propanol was prepared by reduction of methyl α-methoxypropionate by lithium aluminum hydride according to the above procedure. B.p., 125° /700 mm. Lit. b.p. 130° (115)

2-isoPropoxy-1,3-propanediol was prepared by reduction of the 'mixed' esters of isopropoxy malonic acid by lithium aluminum hydride. B.p. 93°/2 mm. n_D^{25}. 1.4430.

Calc. for $C_6H_{14}O_3$: C, 53.73 : H, 10.45

Found : C, 53.28 : H, 10.11

2-isoPropoxy-1-propanol was prepared by lithium aluminum hydride reduction of isopropyl α-isopropoxypropionate according to the aforementioned procedure. B.p., 141-2°/700 mm. Lit. b.p., 143-4° (113).

3-Ethoxy-1-propanol was prepared in 34% yield by lithium aluminum hydride reduction of ethyl β-ethoxypropionate. B.p., 155° /700 mm. Lit. b.p., 161° (119).

3-Methoxy-1-butanol was prepared in 58% yield by reduction of methyl β-methoxybutyrate with lithium aluminum hydride. B.p., 86° /50 mm. Lit. b.p., 159-60° (120).

3-isoPropoxy-1-butanol was prepared in 70% yield by lithium aluminum hydride reduction of isopropyl β-isopropoxybutyrate. B.p., 93°/35 mm. n_D^{25}. 1.4156.

Calc. for $C_7H_{16}O_2$: C, 63.64 : H, 12.12

Found : C, 64.04 : H, 12.17

2-Methoxy-2-methyl-1-propanol was prepared in 82% yield by lithium aluminum hydride reduction of α-methoxyisobutyric acid. B.p., 137°/700 mm. Lit. b.p., 141^{c} (121)

2-Ethoxy-2-methyl-1-propanol was prepared in 56% yield by reduction of α-ethoxyisobutyric acid with lithium aluminum hydride. B.p., 140°/700 mm. Lit b.p, 146-8° (121).

2-isoPropoxy-2-methyl-1-propanol was prepared in 53% yield by lithium aluminum hydride reduction of α-isopropoxyisobutyric acid. B.p. 147-9°. Lit b.p., 42-6°/10 mm. (122).

2-Benzyloxy-2-methyl-1-propanol was prepared in 78% yield by reduction of α-benzyloxyisobutyric acid with lithium aluminum hydride. B.p., 102°/3.5 mm. n_D^{25}. 1.5088.

Calc. for $C_{11}H_{16}O_2$: C, 73.33 : H, 8.89

Found : C, 73.58 : H, 8.90

1-Methoxy-2-methyl-2-propanol was prepared according to the method described in the literature by Palomaa (123) by treatment of ethyl methoxyacetate with methyl magnesium iodide as illustrated below.

Ethyl methoxyacetate (19.7 g. 0.167 mole) was slowly added to an ethereal solution of methyl magnesium iodide prepared from methyl iodide (52.0 g. 0.37 mole) and magnesium (8.9 g., 0.37 mole) in 200 ml. of ether. After addition of the ester was complete, the reaction mixture was stirred for 3 hours and then crushed ice was added to decompose the complex. After filtration, to remove the inorganic solid, the ethereal solution was dried over anhydrous magnesium sulphate, the ether removed by distillation and the residual oil purified by distillation to give 3.7 g. (21%) of material which boiled at 112-5°/700 mm. Lit. b.p., 116.6° (123).

1-Ethoxy-2-methyl-2-propanol was prepared according to the procedure described immediately above. Commencing with ethyl ethoxyacetate and methyl magnesium iodide, a yield of 40% of product was obtained that boiled at 125°/700 mm. Lit. b.p., 129-130° (121).

1-isoPropoxy-2-methyl-2-propanol was prepared in 37% yield from isopropyl isopropoxyacetate and methyl magnesium iodide by the procedure described above. B.p., 75°/70 mm. n_D^{25} 1.4055.

Calc. for $C_7H_{16}O_2$: C, 63.64 : H, 12.12

Found : C, 63.57 : H, 12.14

1-Benzyloxy-2-methyl-2-propanol was prepared in 46% yield from ethyl benzyloxyacetate and methyl magnesium iodide by the above method. B.p., 106°/6 mm. n_D^{25} 1.4997.

Calc. for $C_{11}H_{16}O_2$: C, 73.33 : H, 8.89

Found : C, 73.70 : H, 9.12

2-Methoxy-2-phenylethanol was prepared by the method described by Reeve and Christoffel (124).

(Epoxyethyl)benzene (36 g., 0.3 mole) was added to cooled and stirred methanol (150 ml.) to which 2 drops of concentrated sulphuric acid had been added. The resulting mixture was allowed to stand overnight and then poured into cold water. The product was extracted with ether and the etheral extract dried over anhydrous sodium carbonate. Removal of the ether by distillation afforded an oil which was purified by distillation under reduced pressure to give 33 g. (72%) of material which boiled at 107-8°/6 mm. Lit. b.p., 134°/30 mm. (124)

2-isoPropoxy-2-phenylethanol was prepared by the same procedure as that described above. Commencing with (epoxyethyl)benzene and 2-propanol a 54% yield of the required material was obtained which boiled at 94°/3 mm. n_D^{25}. 1.4982.

Calc. for $C_{11}H_{16}O_2$: C, 73.33 : H, 8.89

Found : C, 73.51 : H, 8.72

2-Methoxy-1-phenylethanol was prepared by the method advocated by Reeve and Christoffel (124).

(Epoxyethyl)benzene (25 g., 0.21 mole) was added to a solution of sodium methoxide (from 1.0 g. of sodium) in 70 ml. of methanol. The reaction mixture was allowed to stand overnight and then refluxed for 4 hours before pouring into cold water. The product was extracted with ether and dried over anhydrous magnesium sulphate. Removal of the solvent, by distillation, afforded

an oil which upon distillation under reduced pressure afforded 24 g. (76%) of material which boiled at 108-110°/6 mm. Lit. b.p., 137-8°/30 mm. (124).

G.l.c. analysis of this product revealed the presence of a small amount of the isomeric 2-methoxy-2-phenylethanol. This was removed by dissolving the product in skellysolve and adding sodium metal (1.2 g.). The precipitated sodium derivative was removed by chromotography on an alumina column using skellysolve as eluant. Removal of the solvent from the eluate afforded the desired material which g.l.c. analysis showed to be $>$99% pure.

2-isoPropoxy-1-phenylethanol was prepared by a similar procedure to that described above. Commencing with (epoxyethyl)benzene and 2-propanol, a yield of 24% of the required material was obtained. B.p., 96°/3 mm. n_D^{25}. 1.4995.

Calc. for $C_{11}H_{16}O_2$: C, 73.33 : H, 8.89

Found : C, 73.14 : H, 8.76

2-β-Chloroethoxyethanol was prepared by acid catalysed alcoholysis of 1,2-epoxyethane after the method advocated in the literature by Lucas et al. (86) and as described below.

1,2-Epoxyethane (8.8 g., 0.2 mole) was slowly added to β-chloroethanol (16 g., 0.2 mole) containing 1 ml. of concentrated sulphuric acid. The resulting mixture was allowed to stand at 25° for 48 hours, then poured into a saturated aqueous solution of sodium carbonate. The product was extracted with ether, the

ether extract was dried over anhydrous sodium carbonate and, after removal of the solvent by distillation, the residual oil was fractionally distilled under reduced pressure. There was obtained 2.8 g. (11%) of product which boiled at 70°/3 mm. Lit. b.p., 180-185° (125).

IV Reduction of 1,3-Dioxolanes and 1,3-Dioxanes with Lithium Aluminum Hydride and Aluminum Chloride.

The same reduction procedure was employed throughout the course of this work. This procedure is exemplified by the following description of the reduction of 2,2-dimethyl-4-phenyl-1,3-dioxolane.

1. The Reduction of 2,2-Dimethyl-4-phenyl-1,3-dioxolane with Lithium Aluminum Hydride and Aluminum Chloride.

2,2-Dimethyl-4-phenyl-1,3-dioxolane (18.0 g., 0.1 mole) was added to a stirred suspension of lithium aluminum hydride (3.9 g., 0.1 mole) in 300 ml. of diethyl ether. The resulting suspension was stirred whilst a solution of aluminum chloride (13.35 g. 0.1 mole) was added in a dropwise manner. The reaction mixture was stirred for one hour after complete addition of the chloride, which usually took about 10 minutes and then cold water was cautiously added to decompose the aluminum complexes and excess hydride. The inorganic material was removed by filtration and the ethereal filtrate dried over anhydrous magnesium sulphate. Removal of the ether afforded an oil which g.l.c. analysis showed to be a mixture consisting of 2-*iso*propoxy-2-phenylethanol (52%) and 2-*iso*propoxy-1-

phenylethanol (48%). The product of the reduction distilled over the range 90-92°/3 mm. Yield:- 14.7 g. (81%).

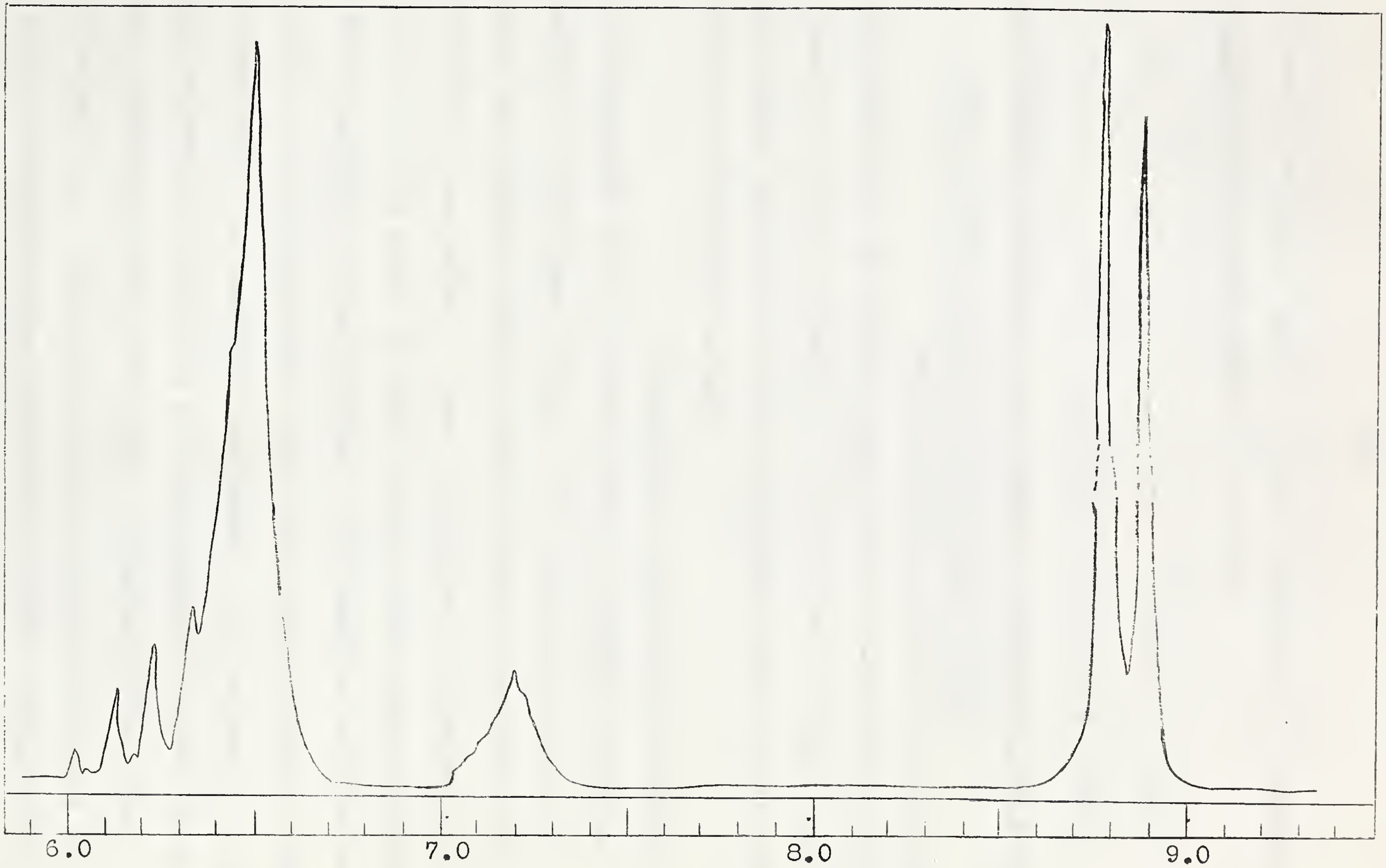
In the following case only, the products of the reduction were separated and characterised singly. This was necessitated by the unavailability of one of the reduction products viz. 3-chloro-2-isopropoxy-1-propanol.

2. Reduction of 4-Chloromethyl-2,2-dimethyl-1,3-dioxolane with Lithium Aluminum Hydride and Aluminum Chloride.

4-Chloromethyl-2,2-dimethyl-1,3-dioxolane (40 g., 0.27 mole) was reduced by the procedure described immediately above to afford 36.0 g. (86%) of reduction product.

G.l.c. analysis of the product showed it to be a mixture consisting of 95% of 1-chloro-3-isopropoxy-2-propanol and 5% of a second material which was assumed to be 3-chloro-2-isopropoxy-1-propanol.

The two products were separated by careful fractional distillation with a 12" column packed with glass helices. The first fraction (32.0 g.) boiled at 114°/72 mm. and was shown to be 1-chloro-3-isopropoxy-2-propanol by comparison of its g.l.c. retention time and also its N.M.R. spectrum with that of an authentic specimen. The residue (4.0 g.) from the fractionation was purified by passing through the g.l.c. column and then by distillation under reduced pressure to give 1.5 g. of material which boiled at 108°/35 mm. The N.M.R. spectrum and



N.M.R. Spectrum of 3-Chloro-2-isopropoxy-1-propanol (solvent carbon tetrachloride).

(referred to tetramethylsilane)

elemental analysis agreed for the structure of 3-chloro-2-isopropoxy-1-propanol. n_D^{25}. 1.4430.

Calc. for $C_6H_{13}ClO_2$: C, 47.22 : H, 8.52 : Cl, 23.28

Found : C, 46.87 : H, 8.39 : Cl, 23.21

III Parallel Reductions as a Means of Obtaining the Relative Rates of Reduction of Acetals and/or Ketals

The following description of the parallel reduction of cis and trans 2-ethyl-4-methyl-1,3-dioxolanes is a typical example of the general procedure used throughout this work to obtain relative rates of hydrogenolysis of acetals and ketals.

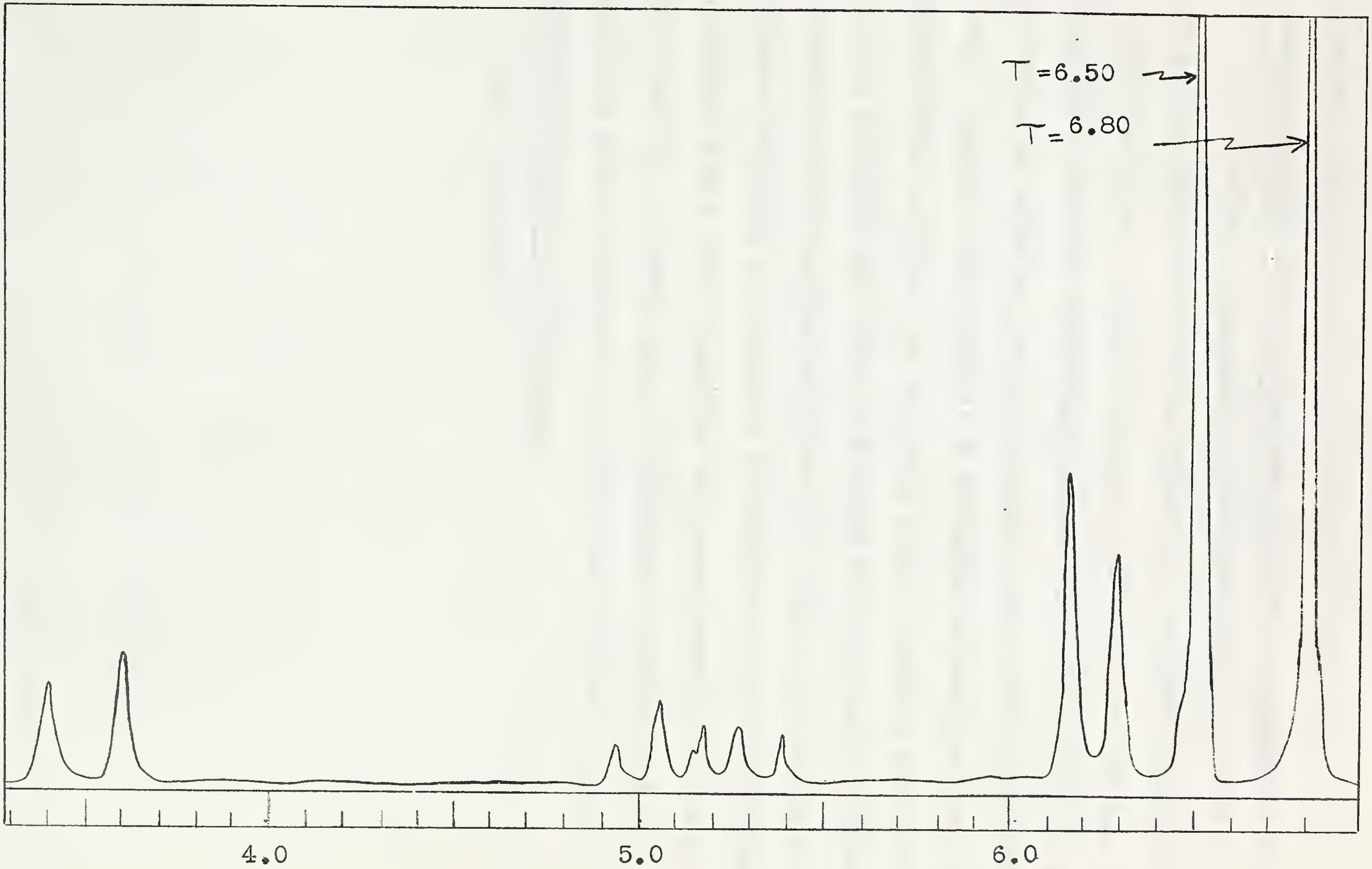
A solution of cis-2-ethyl-4-methyl-1,3-dioxolane (2.9 g., 0.025 mole) and trans-2-ethyl-4-methyl-1,3-dioxolane (2.9 g., 0.025 mole) in 50 ml. of ether was stirred whilst lithium aluminum hydride (0.95 g., 0.025 mole) was added. Then a solution of aluminum chloride (0.7 g., 0.005 mole) in ether (10 ml.) was added dropwise over a period of three minutes. The reaction mixture was stirred for 30 minutes and then water was cautiously added to decompose the aluminum complexes. The inorganic solid was removed by filtration and the etheral filtrate dried over anhydrous sodium carbonate. Removal of the ether afforded 5.4 g. (92%) of material which was analysed by g.l.c. to determine the composition of the product of reduction which was found to consist of 2-n-propoxy-1-propanol (89%) and 1-n-propoxy-2-propanol (11%). G.l.c.

analysis of the unreacted starting material showed it to consist of 62% of the trans isomer and 38% of the cis isomer, thus showing that more of the cis isomer had been reduced than had the trans isomer.

IV Reduction of 1,3,3-Trimethoxy-1-propene with Lithium Aluminum Hydride

1,3,3-Trimethoxy-1-propene (6.6 g. 0.05 mole) in 10 ml. of ether was added dropwise to a stirred suspension of lithium aluminum hydride (1.9 g., 0.05 mole) in ether (50 ml.). The reaction mixture was stirred for 2 hours and then water was cautiously added to decompose the aluminum complexes and excess hydride. After removal of the inorganic solid, by filtration, the ether solution was dried over anhydrous sodium carbonate. Removal of the ether afforded an oil which was distilled under reduced pressure to give 2.3 grams of a colourless liquid which boiled at 64°/96 mm.

The N.M.R. spectrum of this material corresponded for the structure of 1,3-dimethoxy-1-propene. Lit. b.p. 64°/98 mm. (126).



N.M.R. Spectrum of 1,3-Dimethoxy-1-propene (referred to tetramethylsilane) .

The Reduction of 2-Trichloromethyl-1,3-dioxolane with a Combination of Lithium Aluminum Hydride and Aluminum Chloride.

2-Trichloromethyl-1,3-dioxolane(9.5g.,0.05 mole) in 50 ml. of diethyl ether was added to a stirred suspension of lithium aluminum hydride (1.9g., 0.05 mole) in 100 ml. of diethyl ether.The resulting mixture was stirred whilst a solution of aluminum chloride(6.7g., 0.05 mole) in diethyl ether (40 ml.) was added in a dropwise manner.The reaction mixture was stirred for 48 hours after complete addition of the chloride and then cold water was cautiously added to decompose the aluminum complexes and excess hydride.The inorganic material was removed by filtration and the ethereal filtrate dried over magnesium sulphate.Removal of the ether afforded an oil whose g.l.c. retention time and N.M.R. spectrum were identical to those of an authentic sample of 2-dichloromethyl-1,3-dioxolane.

Yield. 5.9g.(76%).

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